

ORIGINAL ARTICLE

Quadrupling Inhaled Glucocorticoid Dose to Abort Asthma Exacerbations

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ABSTRACT

BACKGROUND

Asthma exacerbations are frightening for patients and are occasionally fatal. We tested the concept that a plan for patients to manage their asthma (self-management plan), which included a temporary quadrupling of the dose of inhaled glucocorticoids when asthma control started to deteriorate, would reduce the incidence of severe asthma exacerbations among adults and adolescents with asthma.

METHODS

We conducted a pragmatic, unblinded, randomized trial involving adults and adolescents with asthma who were receiving inhaled glucocorticoids, with or without add-on therapy, and who had had at least one exacerbation in the previous 12 months. We compared a self-management plan that included an increase in the dose of inhaled glucocorticoids by a factor of 4 (quadrupling group) with the same plan without such an increase (non-quadrupling group), over a period of 12 months. The primary outcome was the time to a first severe asthma exacerbation, defined as treatment with systemic glucocorticoids or an unscheduled health care consultation for asthma.

RESULTS

A total of 1922 participants underwent randomization, of whom 1871 were included in the primary analysis. The number of participants who had a severe asthma exacerbation in the year after randomization was 420 (45%) in the quadrupling group as compared with 484 (52%) in the non-quadrupling group, with an adjusted hazard ratio for the time to a first severe exacerbation of 0.81 (95% confidence interval, 0.71 to 0.92; $P=0.002$). The rate of adverse effects, which were related primarily to local effects of inhaled glucocorticoids, was higher in the quadrupling group than in the non-quadrupling group.

CONCLUSIONS

In this trial involving adults and adolescents with asthma, a personalized self-management plan that included a temporary quadrupling of the dose of inhaled glucocorticoids when asthma control started to deteriorate resulted in fewer severe asthma exacerbations than a plan in which the dose was not increased. (Funded by the Health Technology Assessment Programme of the National Institute for Health Research; Current Controlled Trials number, ISRCTN15441965.)

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ASTHMA IS ONE OF THE MOST COMMON chronic diseases, with an estimated 300 million people affected worldwide.¹ Acute exacerbations of asthma are frightening for patients, cause considerable illness and death, and account for a large proportion of the overall costs related to asthma.²

Although plans for patients to manage their asthma (self-management plans) have been shown to improve asthma control,³ the previously recommended step of doubling the dose of inhaled glucocorticoids when asthma control is deteriorating is ineffective at preventing acute exacerbations.^{4,5} Although some guidelines suggest a greater increase in the dose of inhaled glucocorticoids, a 2016 Cochrane review concluded that it is unlikely that increasing the dose of inhaled glucocorticoids reduces the odds of systemic glucocorticoid use or hospitalization or shortens recovery time.⁶

A large, pragmatic trial was therefore commissioned by the Health Technology Assessment Programme of the National Institute for Health Research in the United Kingdom. We performed an individually randomized, unblinded, pragmatic, multicenter trial involving adults and adolescents to test the hypothesis that a self-management plan that included a temporary increase in the dose of inhaled glucocorticoids by a factor of 4 when asthma control started to deteriorate would reduce the use of oral glucocorticoids or unscheduled health care consultations for asthma as compared with a plan that did not include this step.

METHODS

TRIAL OVERSIGHT

The North West–Greater Manchester South NHS Research Ethics Committee approved the protocol. The last author vouches for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol (available with the full text of this article at NEJM.org). Written informed consent was obtained from each participant before inclusion in the trial.

POPULATION

Patients 16 years of age or older with a clinical diagnosis of asthma who were receiving any United Kingdom–licensed dose of inhaled glucocorticoids, with or without add-on medication, and who had had at least one exacerbation leading to treatment with systemic glucocorticoids in the previous 12 months were eligible to participate. (For further details, see the Methods section in the Supplementary Appendix, available at NEJM.org.)

INTERVENTION AND RANDOMIZATION

We compared two self-management plans that were based on a plan developed by Asthma UK and used in the United Kingdom at the time of trial design (Figs. S1 and S2 in the Supplementary Appendix). The plans were identical other than zone 2 of the plans. Zone 1 described well-controlled asthma and recommended continuation of current treatment. Zone 2 described deteriorating asthma control and recommended increased bronchodilator medication and an increase in the dose of inhaled glucocorticoids by a factor of 4 (quadrupling group) or increased bronchodilator medication alone (non-quadrupling group) (Table 1). (For details, see the Methods section in the Supplementary Appendix and the protocol.⁷) Zones 3 and 4 described the development of an exacerbation and when to start oral glucocorticoids and seek medical intervention (zone 3) and what to do in the event of a life-threatening exacerbation (zone 4). Participants were sent an automated text message every month to remind them to follow their self-management plan. Additional glucocorticoid inhalers that were required to achieve a quadrupling of the dose were provided free of charge.

A Web-based randomization system was used to assign participants to the quadrupling group or non-quadrupling group in permuted blocks of randomly varying size. Randomization was stratified according to trial site (regional center), current smoking status (yes vs. no), and maintenance dose of inhaled glucocorticoids (high [$>1000 \mu\text{g}$ per day of beclomethasone or the equivalent] vs. low [$\leq 1000 \mu\text{g}$ per day of beclomethasone or the equivalent]). The participants and local research team were aware of the trial-group assignments at randomization. The trial management group, statistician, and chief investigator were unaware of the trial-group assignments until the analysis was complete. (For details, see the Methods section in the Supplementary Appendix.)

Table 1. Zone 2 of Asthma Self-Management Plans Used by the Two Groups.

Quadrupling Group	Non-Quadrupling Group
Indication of deteriorating asthma control (one or more)	Indication of deteriorating asthma control (one or more)
You need your reliever inhaler more than usual.	You need your reliever inhaler more than usual.
You have more difficulty sleeping because of your asthma.	You have more difficulty sleeping because of your asthma.
Your peak flow is below [80% of your normal level].	Your peak flow is below [80% of your normal level].
Action	Action
Use your reliever inhaler to relieve your symptoms and quadruple your inhaled glucocorticoid dose as described.	Use your reliever inhaler to relieve your symptoms and continue your inhaled glucocorticoid medication at your normal dose.
Once your symptoms or peak flow have returned to normal or after a maximum of 14 days, return to your normal treatment.	
If your symptoms get worse, follow Zone 3 instructions.	If your symptoms get worse, follow Zone 3 instructions.
Start to record your morning peak flow, symptoms, and medication in the trial diary.	Start to record your morning peak flow, symptoms, and medication in the trial diary.
Telephone your research nurse to arrange a trial visit.	Telephone your research nurse to arrange a trial visit.

OUTCOME MEASUREMENTS

The primary outcome was the time to a first severe asthma exacerbation, defined as treatment with systemic glucocorticoids or an unscheduled health care consultation for asthma. Scheduled visits occurred at 6 months and 12 months after randomization. For participants who were lost to follow-up, site staff attempted to review electronic patient records to document whether they had had an asthma-related general-practice appointment or had been prescribed systemic glucocorticoids during the trial period.

Secondary outcomes included the number of participants who had a severe exacerbation, the area under the curve of the morning peak expiratory flow 2 weeks after activation of zone 2 of the self-management plan, the change in score on the Mini Asthma Quality of Life Questionnaire (Mini-AQLQ; scores range from 1 to 7, with higher values indicating better quality of life; minimal important difference, 0.5)⁸ 2 weeks after activation of zone 2 of the self-management plan, and the cumulative dose of inhaled and systemic glucocorticoids used in the 12 months after randomization. (For details, see the Methods section in the Supplementary Appendix.)

SAFETY

Adverse events and serious adverse events relating to established adverse effects of inhaled glucocorticoids were reported during the 14 days after activation of zone 2 of the self-management plan. After a request from the data monitoring

committee, cases of pneumonia were reported for up to 4 weeks after activation of zone 2.

STATISTICAL ANALYSIS

A group of local general practitioners, asthma nurses, and asthma experts suggested that a reduction of one third in the number of people initiating a course of systemic glucocorticoids is a worthwhile treatment effect. With 1000 participants per group, a log-rank test (at the two-sided 5% significance level) had at least 90% power to detect a between-group difference of 30% (relative effect), with the assumption of an exacerbation rate of 13% in the non-quadrupling group.^{4,9} We initially proposed to recruit 2300 patients to allow for withdrawals and losses to follow-up, but this was reduced in March 2015 to a minimum of 1774 because the combined primary-outcome rate was higher than expected. (For details, see the section on sample size in the protocol.⁷)

All analyses were conducted with the use of Stata software, version 13.1 (StataCorp). Cox proportional-hazards regression was used to analyze the primary outcome, including the randomization-stratification variables, the dose of inhaled glucocorticoids (high vs. low), and smoking status (never smoked vs. former smoker vs. current smoker) as covariates and using a shared-frailty model to account for stratification according to regional center. Participants were included in analyses according to their randomized group, regardless of their adherence to their

assigned self-management plan. All the participants were included in the analysis of the primary outcome, except for those who had no further contact after randomization and had no data on systemic glucocorticoid use or unscheduled health care consultations for asthma. A sensitivity analysis that included all the participants was performed. (For details, see the Methods section in the Supplementary Appendix.)

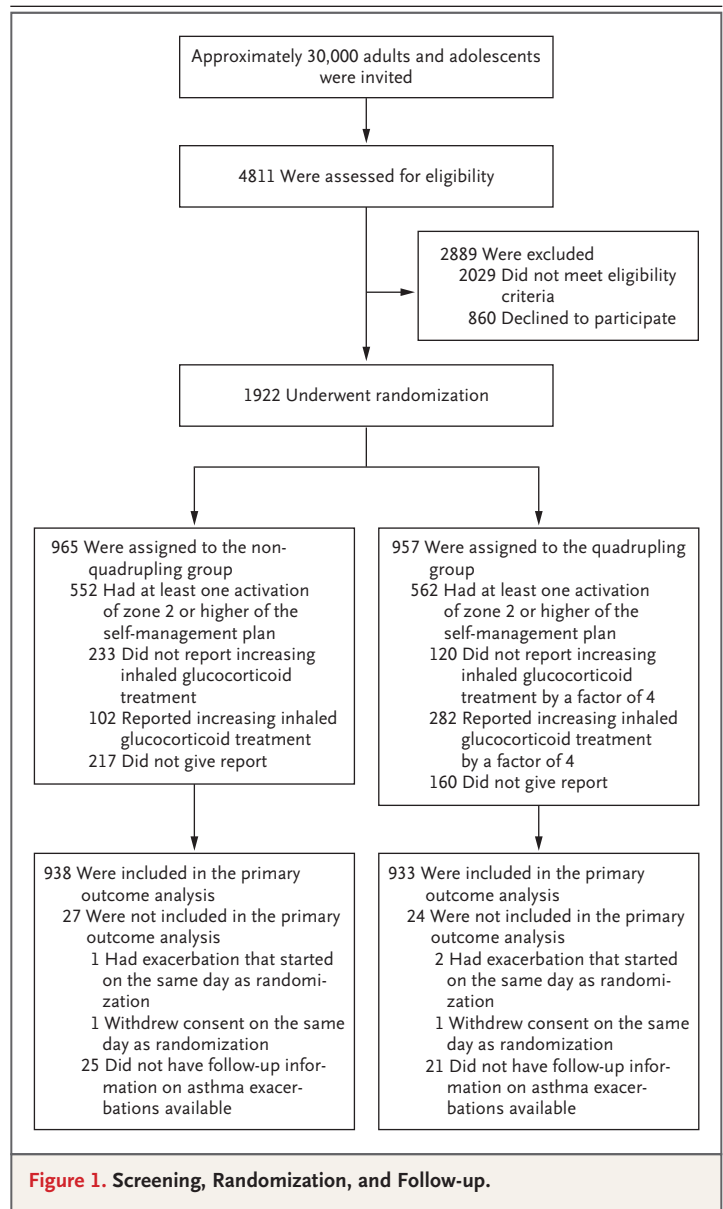
RESULTS

PARTICIPANTS

We wrote to approximately 30,000 potential patients from general-practice and volunteer databases and also used posters, social media, and face-to-face discussions in clinics to recruit patients. A total of 4811 patients were screened, of whom 1922 underwent randomization (957 to the quadrupling group and 965 to the non-quadrupling group). All the participants received their assigned self-management plan, although 51 (3%) were excluded from the primary analysis, primarily owing to being lost to follow-up and having no outcome data. A total of 933 participants in the quadrupling group and 938 participants in the non-quadrupling group were included in the primary analysis (Fig. 1). Participants were enrolled from May 2013 through January 2016, and follow-up was completed by March 2017.

A total of 81% of recruited participants were identified in primary care and 19% in secondary care. The mean (\pm SD) age of the participants was 57 ± 15 years, 1305 participants (68%) were female, 1495 (78%) were receiving 1000 μ g or less per day of beclomethasone (or equivalent glucocorticoid), and 1344 (70%) were using a long-acting beta-agonist-inhaled glucocorticoid combination inhaler at the time of randomization. A total of 1116 participants (58%) had never smoked, 125 (7%) were current smokers, and 681 (35%) were former smokers. Characteristics at baseline were well balanced between the two treatment groups (Table 2).

Attendance at the scheduled visits was similar in the two groups. A total of 773 participants (81%) in quadrupling group and 772 (80%) in the non-quadrupling group attended the 6-month visit, and 679 (71%) and 700 (73%), respectively, attended the 12-month visit.



OUTCOMES

Of the 1922 participants, 1114 (58%) reached zone 2 or higher of their self-management plan at some point during follow-up (562 participants in the quadrupling group and 552 participants in the non-quadrupling group). The number of participants who reported a severe exacerbation of asthma in the year after randomization was 420 (45%) in the quadrupling group as compared with 484 (52%) in the non-quadrupling group, yielding an adjusted hazard ratio for the time to a first exacerbation of 0.81 (95% confidence in-

Table 2. Baseline Characteristics of the Participants.*

Characteristic	Non-Quadrupling Group (N=965)	Quadrupling Group (N=957)
Age — yr		
Mean	56.7±15.2	56.2±15.5
Range	19–94	16–91
Sex — no. (%)		
Male	316 (33)	301 (31)
Female	649 (67)	656 (69)
Source of recruitment — no. (%)		
Primary care	774 (80)	785 (82)
Secondary care	191 (20)	172 (18)
Mean peak expiratory flow at screening — liters/min	381.1±112.2	386.9±110.8
Type of inhaler — no. (%)		
Glucocorticoid	303 (31)	275 (29)
Combination	662 (69)	682 (71)
Type of inhaled glucocorticoid — no. (%)		
Beclomethasone	388 (40)	325 (34)
Budesonide	220 (23)	225 (24)
Fluticasone	350 (36)	401 (42)
Ciclesonide	7 (1)	6 (1)
Maintenance dose of inhaled glucocorticoids		
Median (IQR) — $\mu\text{g/day}$ of beclomethasone or equivalent	800 (400–1000)	800 (400–1000)
Range — $\mu\text{g/day}$ of beclomethasone or equivalent	100–4000	80–4000
Low: $\leq 1000 \mu\text{g/day}$ of beclomethasone or equivalent — no. (%)	752 (78)	743 (78)
High: $>1000 \mu\text{g/day}$ of beclomethasone or equivalent — no. (%)	213 (22)	214 (22)
Smoking status — no. (%)		
Never smoked	552 (57)	564 (59)
Current smoker	66 (7)	59 (6)
Former smoker	347 (36)	334 (35)
Pack-years among current or former smokers		
No. of participants	413	393
Mean pack-yr	13.9±16.1	12.3±14.5
Mini-AQLQ overall score†		
No. of participants	959	944
Mean score	5.0±1.2	5.1±1.2
Mini-AQLQ symptom score†		
No. of participants	954	938
Mean score	4.8±1.3	4.9±1.3

* Plus-minus values are means \pm SD. Percentages may not add up to 100 because of rounding. IQR denotes interquartile range.

† Scores on the Mini Asthma Quality of Life Questionnaire (Mini-AQLQ) range from 1 to 7, with higher scores indicating a better quality of life. For the Mini-AQLQ overall score, a within-patient change of 0.5 represents the minimal important difference.

terval [CI], 0.71 to 0.92; $P=0.002$) (Fig. 2). Additional adjustment for age, sex, and peak flow at randomization had little effect on the hazard ratio (0.80; 95% CI, 0.71 to 0.92; $P=0.001$). There was also little difference in the hazard ratio according to smoking status or dose of inhaled glucocorticoids (high vs. low) at randomization (Table S1 in the Supplementary Appendix). A sensitivity analysis that included all 1922 participants yielded a hazard ratio for the time to a first exacerbation of 0.81 (95% CI, 0.72 to 0.92).

The percentage of participants who used systemic glucocorticoids was lower in the quadrupling group than in the non-quadrupling group, as was the percentage of participants who had unscheduled health care consultations for asthma. A total of 311 participants (33%) in the quadrupling group versus 377 (40%) in the non-quadrupling group started systemic glucocorticoids, with a mean number of courses of 0.50 versus 0.61 (incidence rate ratio, 0.82; 95% CI, 0.70 to 0.96). A total of 379 participants (41%) in the quadrupling group versus 442 (47%) in the non-quadrupling group had an unscheduled health care consultation, with a mean total number of visits of 0.73 versus 0.84 (incidence rate ratio, 0.86; 95% CI, 0.75 to 0.99). (For details, see Tables S2 and S3 in the Supplementary Appendix.)

Self-reported adherence to the instruction to quadruple or to not adjust the dose of inhaled glucocorticoids was similar in the two groups. Among participants with a reported activation of zone 2, 50% of those in the quadrupling group and 42% of those in the non-quadrupling group were judged by the researcher as having good adherence, and 6% and 3%, respectively, were judged as having poor adherence. No information was available for 28% and 39% of the participants in the respective groups.

Approximately 47% of the participants had a peak-flow value recorded on activation of zone 2 of their self-management plan and at least one value on or after day 10 (54% of those in the quadrupling group and 41% of those in the non-quadrupling group). From these values, the mean area under the curve of the peak flow was 1166 liters per minute per day in the quadrupling group and 1130 liters per minute per day in the non-quadrupling group (adjusted difference in

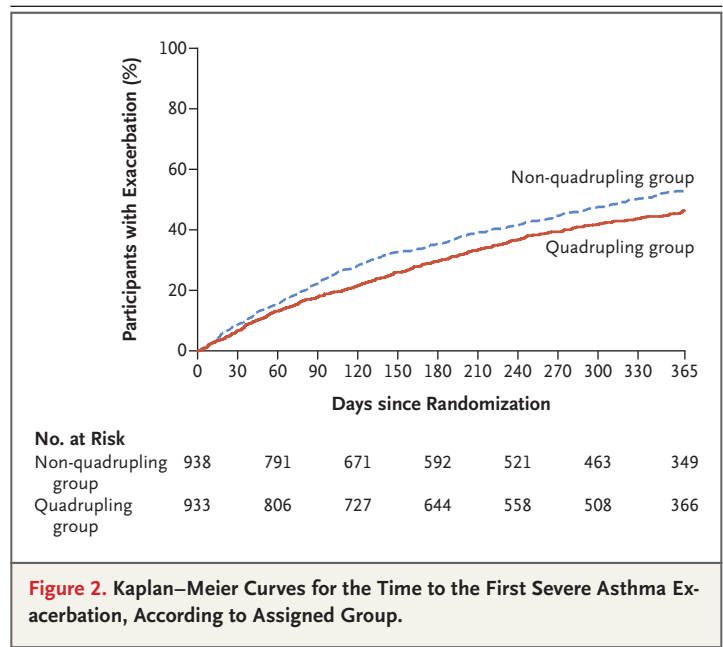


Figure 2. Kaplan–Meier Curves for the Time to the First Severe Asthma Exacerbation, According to Assigned Group.

means, 38 liters per minute per day; 95% CI, 13 to 62; 529 participants) (Table S4 in the Supplementary Appendix). Similarly, Mini-AQLQ data after the first activation of zone 2 was available for only 45% of the participants, with data available for more participants in the quadrupling group than in the non-quadrupling group (50% vs. 39%). The mean Mini-AQLQ score 2 weeks after zone 2 activation was also higher in the quadrupling group, with an adjusted difference in means of 0.20 (95% CI, 0.03 to 0.46; 499 participants) (Table S4 in the Supplementary Appendix).

Among participants who attended the 12-month follow-up visit, the estimated mean total dose of inhaled glucocorticoids taken in the 12 months after randomization was 385 mg in the quadrupling group (679 participants) and 328 mg in the non-quadrupling group (700 participants). The mean total dose of systemic glucocorticoids was 121 mg and 151 mg, respectively.

In the 14 days after zone 2 activation, 11 participants (2%) in the quadrupling group (9 receiving a high maintenance dose of inhaled glucocorticoids) reported a total of 11 serious adverse events, and 22 participants (4%) in the non-quadrupling group (8 receiving a high maintenance dose of inhaled glucocorticoids) reported a total of 32 serious adverse events. The most

common serious adverse event was hospitalization for asthma, occurring 3 times in the quadrupling group and 18 times in the non-quadrupling group. Because these events also fulfill the criteria for the primary outcome, they are included in the primary outcome analysis, so caution is needed when considering total adverse events in the two groups. There were 5 events in the quadrupling group and 6 in the non-quadrupling group relating to pneumonia or lower respiratory tract infection in the 4 weeks after activation of zone 2 of the self-management plan. One participant in the quadrupling group died of severe pneumonia. (For details, see the Supplementary Appendix.)

In the 14 days after zone 2 activation, 41 participants (7%) in the quadrupling group reported a total of 56 nonserious adverse events, and 10 participants (2%) in the non-quadrupling group reported a total of 13 nonserious adverse events. Oral candidiasis and dysphonia accounted for the great majority of nonserious adverse events, with 36 events in the quadrupling group (19 events of oral candidiasis) and 9 events in the non-quadrupling group (7 events of oral candidiasis).

DISCUSSION

Our trial involving adults and adolescents showed that a temporary quadrupling of the dose of inhaled glucocorticoids at the time of worsening asthma control resulted in a lower rate of severe exacerbations of asthma than no increase in the dose (45% vs. 52%). The main strength of our trial is its pragmatic design and 80% recruitment in primary care, giving it considerable external validity. Broad inclusion criteria ensured that the trial results are applicable to adult patients with a clinical diagnosis of asthma who are taking any licensed dose of inhaled glucocorticoids, with or without add-on medication and regardless of smoking status. We minimized trial visits after training participants to follow a personalized self-management plan to reflect follow-up in clinical practice as closely as possible, although the requirement to report zone 2 activations is different than real-life clinical practice and may have influenced adherence to the assigned self-management plan. Finally, we chose a primary outcome that was directly relevant to the trial participants, and owing to the time-to-event analysis, only 3% of the participants could not be included in the primary analysis.

The pragmatic design of our trial may also be considered to limit the implications of its findings. The open-label nature of the intervention means that there may be a bias because the participants were aware, and many of the treating physicians may have been aware, of the person's intervention, and this may have influenced the decision by participants to seek medical help or by physicians to advise treatment with systemic glucocorticoids. If such an effect occurred, it reflects the beneficial effects likely to be seen in clinical practice that are missed in strict explanatory studies. The pragmatic nature of the trial also affected the quality of secondary outcome data such as the number of peak-flow measurements and quality-of-life questionnaires completed, but the data that were collected were consistent with better asthma control in the quadrupling group. A further potential bias was that more participants in the quadrupling group than in the non-quadrupling group attended a post-activation visit and, therefore, provided diary-card data; the extent to which this affected the outcomes observed is unknown.

The estimated rate of severe exacerbations was deliberately conservative, to ensure adequate power, and was based on our previous studies, in which participants did not have to have had an exacerbation leading to the use of systemic glucocorticoids in the previous 12 months.^{4,9} In reality, the rate of severe exacerbations was much higher in the non-quadrupling group than we estimated, enabling a reduction in the number of participants required for the trial to detect a 30% effect size without a loss of statistical power. Our finding that approximately 50% of the patients included in the trial had an exacerbation, within a year, that led to treatment with oral glucocorticoids or an unscheduled health care consultation confirms that our inclusion criteria identified a group of patients at high risk for an asthma exacerbation and is consistent with generally poor asthma control reported in many asthma surveys.^{10,11} It also highlights the pragmatic nature of our trial, because the exacerbation rate was much higher than that seen in more explanatory trials in which patient selection, a high degree of follow-up care, and a high rate of adherence to medication are all likely to reduce the background exacerbation rate.

Previous studies of self-management plans have shown that provision of a written self-

management plan based on symptoms or peak-flow recordings improves asthma control and reduces the incidence of exacerbations and hospital visits as compared with no self-management plan.³ We and others have, however, found that the previous recommendation to double the dose of inhaled glucocorticoids when asthma control is deteriorating was no more effective than not changing the dose,^{4,5} and a 2016 Cochrane review concluded that it is unlikely that increasing the dose of inhaled glucocorticoids reduces the odds of systemic glucocorticoid use or hospitalization or shortens recovery time.⁶ When we designed our trial, a 30% reduction in the incidence of asthma exacerbations was thought to be a minimum that was clinically meaningful. Although we observed a significant 19% reduction in the incidence of severe exacerbations, the magnitude of reduction was smaller than expected.

We believe that our safety data support the clinical benefit of temporarily quadrupling the dose of inhaled glucocorticoids, because participants in the quadrupling group reported fewer asthma-related hospitalizations than those in the non-quadrupling group (3 vs. 18). However, the bias of the open-label aspect of the trial may have altered the threshold to hospitalize participants and cannot be measured.

As expected, the quadrupling group had a higher frequency of treatment-related adverse effects, such as oral candidiasis that led to treatment with topical antifungal medication. We paid particular attention to the issue of pneumonia because of reports of pneumonia associated with the use of inhaled glucocorticoids in asthma¹² and chronic obstructive pulmonary disease,¹³ but there was no significant between-group difference in the incidence of pneumonia in our trial. The median dose of inhaled glucocorticoids in our trial was 0.8 mg per day, so quadrupling this would be approximately equivalent

to 3.2 mg per day of inhaled beclomethasone for 7 to 14 days. Unfortunately, the systemic effects of high-dose inhaled glucocorticoids are not well understood. In terms of milligrams of prednisolone, adrenal suppression from 1.0 mg per day of budesonide has been estimated to be as high as that from 8.7 mg of prednisolone.¹⁴ Because we included patients receiving 1.6 mg of inhaled budesonide and 2 mg of inhaled fluticasone propionate, and if the potency ratio between inhaled glucocorticoids and prednisolone is linear, then the quadrupled dose in these participants could have had the same systemic effects on adrenal suppression as a course of prednisolone that is used to treat severe asthma exacerbations.

In our trial, the number of patients who needed to be provided with such a self-management plan in order to prevent one severe asthma exacerbation was 15 (95% CI, 9 to 43). Given the potential benefit with respect to preventing exacerbations and in view of the toxic effects of inhaled glucocorticoids and the biases that may have been introduced by the absence of blinding, individual practitioners, patients, and guideline committees will need to consider whether the magnitude of the reduction achieved is clinically meaningful.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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