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## **Pilot study: The effect of reducing treatment on exercise induced bronchoconstriction.**

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**Pilot study: The effect of reducing treatment on exercise induced bronchoconstriction.**

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56  
57 **Abbreviated Title:** Treatment reduction and EIB  
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Treatment reduction and EIB

## Abstract

**Rationale:** Asthma therapy should be stepped up or stepped down in response to changes in asthma control. However, there is little evidence available on the optimal timing, sequence and degree of medication reductions. In this study we analyzed clinically stable asthmatic children who underwent a medication reduction from a combination preparation consisting of an inhaled corticosteroid (ICS) and long acting beta2-agonists (LABA) to monotherapy with the same dose of the ICS. We hypothesized that the extent of exercise induced bronchoconstriction (EIB) would not increase after the cessation of the LABA.

**Methods:** 19 children, aged 8-16 years, with clinically stable asthma, receiving ICS/LABA combination therapy, were analyzed in this open-label pilot study. Children performed an exercise challenge at baseline and 3 weeks after the medication reduction. Best values of spirometric measurements of the forced expiratory volume in 1 second (FEV<sub>1</sub>) were used for statistical calculations.

**Results:** Maximum percent fall in FEV<sub>1</sub> was significantly lower after 3 weeks of ICS monotherapy ( $p = 0.03$ ). 8/19 children had a  $\geq 15\%$  fall in FEV<sub>1</sub> after exercise at the initial exercise test. In this subgroup, maximum percent fall in FEV<sub>1</sub> after the medication reduction was significantly lower ( $p < 0.01$ ), and in 6 children it decreased to  $< 15\%$ , indicating they no longer had EIB.

**Conclusion:** In clinically stable asthmatic children on ICS/LABA combination therapy, the cessation of the LABA can reduce and in most cases abolish EIB.

**Keywords:** asthma, children, long acting bronchodilator agent, inhaled corticosteroid

## Introduction

According to international guidelines, asthma therapy should be stepped up or stepped down in response to changes in asthma control.<sup>1,2</sup> Combination therapy with an inhaled corticosteroid (ICS) and long acting beta2-agonist (LABA) is often prescribed as the third step in treatment regimens.<sup>1,2</sup> There are many arguments in favor of this combination.<sup>3</sup> A meta-analysis reviewing LABA treatment for childhood asthma concluded that the addition of a LABA to an ICS improved pulmonary function measures, reduced the use of rescue medications and improved quality of life measures.<sup>4</sup> LABAs are also effectively used as prophylaxis for exercise induced bronchoconstriction (EIB).<sup>5-7</sup> EIB occurs in the majority of asthmatic children and is an index of airway hyperresponsiveness (AHR). However, regular use of LABAs can lead to downregulation of the beta2-adrenoreceptor ( $\beta$ 2AR), resulting in the development of tolerance.<sup>8</sup> This implies that the duration of the bronchoprotective effect of a LABA against EIB is reduced.<sup>6,7,9,10</sup> Furthermore, the recovery time from EIB to pre-exercise lung function after rescue therapy with a short-acting beta2-agonist (SABA) is prolonged.<sup>11,12</sup> Regular treatment with SABAs can even enhance the severity of EIB.<sup>11,13</sup>

By reviewing the medical records of asthmatic adults, Yawn et al. found that only 13% of medication changes were step-down changes.<sup>14</sup> Reductions of the dosage were about twice as common as reductions in the class of medication prescribed. There is little evidence available on the optimal timing, sequence and degree of treatment reductions. When asthma is controlled with ICS/LABA combination therapy, the suggested step-down approach is to reduce the dose of the ICS.<sup>15-17</sup> An alternative is to discontinue the LABA and continue ICS monotherapy at the same dose.<sup>1,2</sup> The effect of reducing treatment from ICS/LABA combination therapy to ICS monotherapy on EIB has not yet been studied.

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3 In this study, we analyzed this medication reduction in clinically stable asthmatic children.  
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5 Because the development of tolerance has an impact on the severity of EIB, we hypothesized  
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8 that the extent of EIB would not increase after the cessation of the LABA.  
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For Peer Review

## Materials and Methods

### *Subjects*

Children from the outpatient clinic of the Medisch Spectrum Twente in Enschede, receiving treatment with ICS/LABA combination therapy with clinically stable asthma for > 3 months, who underwent a medication reduction according to treatment guidelines, were asked to participate in this study. Data from twenty otherwise healthy children, aged 8-16 years, were analyzed. Children had to be able to run on a treadmill and perform reproducible spirometry (i.e. variation of percentage of the predicted value in 3 of 5 consecutive measurements < 5%). Their forced expiratory volume in one second (FEV<sub>1</sub>) had to be at least 70% of predicted normal value. Children were required to withhold the use of leukotriene receptor antagonists (LTRAs), intranasal steroids, LABAs and ICSs for 24 hours and SABAs for 8 hours before both exercise challenges. No vigorous exercise was permitted for 4 hours before an exercise challenge.

### *Study Design*

This was an open-label pilot study. Children and their parents were contacted twice, four and two weeks prior to the first visit, to inform them about the importance of medication adherence. During the initial visit all children were asked to fill out Juniper's asthma control questionnaire (ACQ) and pediatric asthma quality of life questionnaire (PAQLQ). They performed an exercise challenge, with pulmonary function tests before and after the challenge, at the local ice rink, Euregio Kunstijsbaan, Enschede. Standard pulmonary function test in this study consisted of a duplicated expiratory flow-volume loop.

After the initial visit treatment was reduced from ICS/LABA combination therapy to monotherapy with the same dose of the ICS. The second visit was scheduled at the local ice Treatment reduction and EIB

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rink within 3 weeks after the first visit. During the second visit children were again asked to fill out both questionnaires and performed a second exercise challenge.

### *Questionnaires*

The ACQ has 7 questions, scoring 5 symptoms, baseline FEV<sub>1</sub> % predicted and daily rescue bronchodilator use. Children can respond to these questions on a 7-point scale (0 = no impairment, 6 = maximum impairment). Baseline FEV<sub>1</sub> % predicted is also scored on a 7-point scale. The questions are equally weighted and the ACQ score is the mean of the 7 questions and therefore between 0 (totally controlled) and 6 (severely uncontrolled).

The PAQLQ has 23 questions in 3 domains; symptoms, activity limitation and emotional function. Children can respond on a 7-point scale (1 = maximum impairment, 7 = no impairment). The total PAQLQ score is the mean of all 23 questions and therefore between 1 (impaired quality of life) and 7 (no impairment in quality of life). Domain scores are the means of the items in those domains.

### *Pulmonary function test*

A MicroLoop® spirometer, in combination with Spida5® software, was used to measure pulmonary volumes and flow-volume loops. The calibration of this spirometer was checked before testing. The expiratory flow-volume loop was recorded by instructing the children to perform a maximal expiratory effort from inspiratory vital capacity to residual volume. All measurements were performed in duplicate. Pulmonary function was calculated from the best curve. FEV<sub>1</sub> was used as an index of airway hyperresponsiveness.



### *Exercise challenge*

Exercise challenge testing was performed by running with nose clipped on a treadmill (Reebok®, TR1 premium run) using the standardized ATS protocol.<sup>18</sup> A constant temperature of 10°C and absolute humidity of 4.2 g/kg was obtained by testing in the local ice rink. Baseline spirometry was performed and the prechallenge FEV<sub>1</sub> documented as the best FEV<sub>1</sub> of two measurements. The test started with running at low speed on the treadmill with an incline of 10%. During the test, heart rate was continuously monitored. The running speed of the treadmill was increased, raising the heart rate to approximately 90% of the predicted maximum ((220-age) x 0.9). This speed was maintained for six minutes. After the exercise challenge, flow volumes were measured at t = 1, 3, 6, 9, 12, 15 and 20 minutes. Maximum percent fall in FEV<sub>1</sub> was used for further analysis. A fall of > 15% in FEV<sub>1</sub> from baseline was considered a positive response.

### *Statistical analysis*

Best values of spirometric measurements of FEV<sub>1</sub> were used for statistical calculations. Data were split into two groups: children with EIB during the initial visit (defined as a > 15% fall in FEV<sub>1</sub> after exercise) and children without EIB. Further calculations were performed on both groups separately and together. The same analysis was performed on children with a > 10% fall in FEV<sub>1</sub> after the initial exercise challenge.

Baseline percent predicted FEV<sub>1</sub> before both challenges were expressed as mean ± SD and compared using Student's paired *t* test. Symptom scores on the ACQ and PAQLQ before both challenges were compared using Wilcoxon's rank test. Maximum percent fall in FEV<sub>1</sub> after both exercise challenges were compared using Student's paired *t* test.

Spearman's rank order correlation coefficient was calculated for the correlation between ACQ and PAQLQ scores and % fall in FEV<sub>1</sub> after exercise.

Treatment reduction and EIB

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## Results

Research population consisted of 20 children. One child was excluded from analysis because he was not able to perform reproducible spirometry. Data from 19 children were used for analysis (table 1). Among them were 13 boys and 6 girls. Mean age ( $\pm$  SD) was  $11.2 \pm 2.8$  years. Fifteen children were using the combination preparation fluticasone/salmeterol (median dose  $400\mu\text{g}$ ) before the first visit and changed to fluticasone monotherapy and 4 children were using the combination preparation budesonide/formoterol (median dose  $400\mu\text{g}$ ) before the first visit and changed to budesonide monotherapy. Six children were on a LTRA and six on an intranasal steroid.

Baseline FEV<sub>1</sub> before the initial exercise challenge had a normal distribution with a mean ( $\pm$  SD) of  $94.1 \pm 13.6\%$  predicted value, which was not significantly different from baseline FEV<sub>1</sub> three weeks after the medication reduction ( $94.6 \pm 15.1\%$  predicted value). After the first exercise challenge, FEV<sub>1</sub> fell to a mean of  $80.6 \pm 15.0\%$  predicted value. After the second exercise challenge, FEV<sub>1</sub> fell to a mean of  $86.4 \pm 16.1\%$  predicted value, which was significantly higher ( $p = 0.025$ ).

Mean maximum heart rate during the first exercise challenge was  $87.6 \pm 4.2\%$  of maximum heart rate, which was not significantly different from mean maximum heart rate during the second challenge ( $87.2 \pm 3.9\%$ ).

Mean maximum percent fall in FEV<sub>1</sub> after the first exercise challenge was  $14.5 \pm 10.4\%$ .

Maximum percent fall in FEV<sub>1</sub> after the second exercise challenge was significantly lower ( $p = 0.03$ ), with a mean of  $9.0 \pm 6.5\%$ . (Figure 1) In 14 children the response to an exercise

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3 challenge, measured by the maximum percent fall in FEV<sub>1</sub>, decreased after the medication  
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5 reduction. In 5 patients the response to an exercise challenge increased.  
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10 There were 8 children on ICS/LABA combination therapy who experienced EIB, defined by a  
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12  $\geq 15\%$  fall in FEV<sub>1</sub> after exercise. This subgroup had a mean maximum percent fall in FEV<sub>1</sub>  
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14 after the first exercise challenge of  $25.1 \pm 6.2\%$ . Maximum percent fall in FEV<sub>1</sub> after the  
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16 second exercise challenge was significantly lower ( $p < 0.01$ ), with a mean of  $11.6 \pm 8.1\%$ .  
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18 (Figure 2, Figure 3) In all 8 children, maximum percent fall in FEV<sub>1</sub> after exercise decreased  
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20 after the medication reduction. In 6 children, maximum percent fall in FEV<sub>1</sub> was  $< 15\%$ ,  
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22 indicating they were no longer experiencing EIB.  
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27 There were 11 children on ICS/LABA combination therapy without EIB (fall in FEV<sub>1</sub>  $<$   
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29  $15\%$ ). In this subgroup, there was no change in mean maximum percent fall in FEV<sub>1</sub> after the  
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31 medication reduction.(Figure 4) Only one child developed a mild EIB (fall in FEV<sub>1</sub>  $17.1\%$ )  
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33 after the medication reduction.  
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38 There were 10 children on ICS/LABA combination therapy with a  $\geq 10\%$  fall in FEV<sub>1</sub>. This  
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40 subgroup had a mean maximum percent fall in FEV<sub>1</sub> after the first exercise challenge of  $22.5$   
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42  $\pm 7.4\%$ . Maximum percent fall in FEV<sub>1</sub> after the second exercise challenge was significantly  
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44 lower ( $p < 0.001$ ) with a mean of  $10.2 \pm 7.4\%$ . (Figure 5, Figure 6) In all 10 children,  
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46 maximum percent fall in FEV<sub>1</sub> after exercise decreased after the medication reduction. In 7  
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48 children, maximum percent fall in FEV<sub>1</sub> was  $< 10\%$  after the medication reduction.  
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55 At the initial visit asthma was generally well controlled with a median [range] score on the  
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57 ACQ of 0.86 [3.00]. The children's quality of life was generally not impaired, with a total  
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59 median [range] score on the PAQLQ at the initial visit of 5.8 [3.60] and a median score in the  
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Treatment reduction and EIB

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3 symptoms domain of 6.0 [2.65]. At the second visit median score on the ACQ was 0.71  
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5 [3.57], which was not significantly different from the initial score. Total and symptom scores  
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7 on the PAQLQ were respectively 6.3 [3.80] and 6.1 [3.65], which were not significantly  
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9 different from the initial scores.  
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12 There was a correlation between scores on the ACQ and PAQLQ (Spearman's rho = 0.43, p =  
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14 0.013). There was no correlation between scores on the ACQ or PAQLQ and maximum  
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16 percent fall in FEV<sub>1</sub> after exercise.  
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## Discussion

In this study, we monitored a medication reduction from ICS/LABA combination therapy to monotherapy with the same dose of the ICS in clinically stable asthmatic children. Mean maximum percent fall in FEV<sub>1</sub> after an exercise challenge was significantly lower ( $p = 0.03$ ) after the medication change and FEV<sub>1</sub> fell to a significantly higher ( $p = 0.025$ ) percentage of predicted value. In a subgroup of 8 children with a  $> 15\%$  fall in FEV<sub>1</sub> after the first exercise challenge, maximum percent fall in FEV<sub>1</sub> reduced in all children after the medication change ( $p < 0.01$ ). Of this subgroup, 6 children had a maximum percent fall in FEV<sub>1</sub>  $< 15\%$  after the second exercise challenge, indicating they were no longer experiencing EIB. This suggests that in asthmatic children on ICS/LABA combination therapy, the cessation of LABA can reduce and in most cases abolish EIB.

To our knowledge, the effect of reducing treatment from ICS/LABA combination therapy to ICS monotherapy on EIB has not yet been studied. According to international guidelines<sup>1,2</sup> treatment choices should be guided by asthma control. Once asthma control is achieved and maintained for at least 3 months, a step down can be considered. When asthma is controlled with ICS/LABA combination therapy, the suggested approach is to reduce the ICS by approximately 25–50 percent every 3 months to the lowest dose possible.<sup>1,2</sup> An alternative is to discontinue the LABA and continue ICS monotherapy at the same dose.<sup>1,2</sup> Reducing the dose of the ICS is considered more effective than switching to an ICS alone.<sup>15-17</sup> The cessation of the LABA could result in a deterioration of asthma control, measured by morning peak expiratory flow (PEF), daily symptoms and bronchodilator use.<sup>15-17</sup> On the contrary, a report by Weinberger et al. describes an example of two adolescent patients whose EIB improved after the replacement of salmeterol with slow-release theophylline.<sup>19</sup>

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6 We analyzed the effect of stepping down treatment on EIB because EIB occurs in the majority  
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8 of asthmatic children and has a great impact on their quality of life.<sup>20</sup> Measuring the airway  
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10 response to exercise can be used as an indicator of AHR, which is indirectly associated with  
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12 airway inflammation. Titrating treatment guided by AHR leads to fewer uncontrolled  
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14 episodes in adults with asthma<sup>21</sup> and prevented a decline in lung function in children with  
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16 asthma.<sup>22</sup> This suggests that AHR is an indirect marker of asthma control.  
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22 A possible setback of this study is the lack of a control group in whom we did not change the  
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24 medication regimen. In this pilot study, we decided to analyze regular medication reductions,  
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26 based on clinical decisions. However, the lack of a control group makes this study susceptible  
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28 to a learning bias, seasonal bias and a bias due to an improvement in adherence to treatment.  
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30 All children were experienced in performing lung function tests. To exclude a seasonal bias,  
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32 this study was performed outside the main pollen season. Second visits were planned  $21 \pm 6$   
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34 days after the first visit. There were no differences between baseline FEV<sub>1</sub> % predicted and  
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36 scores on the ACQ and PAQLQ before both challenges. To optimize adherence, children and  
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38 their parents were informed about its importance four weeks prior to the first exercise  
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40 challenge and again by a telephonic contact two weeks prior to the first exercise challenge. At  
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42 the first visit to the ice rink, they reported an adherence of  $86 \pm 12\%$ .  
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51 A reversal of the previously developed tolerance due to regular use of LABAs could explain  
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53 the reduction in EIB when LABAs were discontinued. Regular use of LABAs leads to  
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55 downregulation of the  $\beta$ 2AR,<sup>8</sup> resulting in a reduction of the duration of the bronchoprotective  
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57 effect of a LABA against EIB<sup>6,7,9,10</sup> and a prolonged recovery time from EIB after rescue  
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59 therapy with a SABA.<sup>11,12</sup> Although corticosteroids increase transcription of the  $\beta$ 2AR-gene,  
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Treatment reduction and EIB

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3 which could theoretically compensate for the downregulation of the  $\beta$ 2AR,<sup>3</sup> tolerance is not  
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5 prevented by the concomitant use of ICSs.<sup>9,12,23,24</sup>  
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10 Regular use of SABAs or LABAs could paradoxically have a pro-inflammatory effect. In  
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12 vitro, incubation of monocytes with increasing doses of terbutaline induced a shift of the  
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14 human Th1-/Th2-type cytokine balance toward a Th2-type response.<sup>25</sup> Incubation of human  
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16 mast cells with formoterol or salmeterol abolished the  $\beta$ 2AR-mediated inhibition of histamine  
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18 release.<sup>26</sup> This indicates that regular exposure to LABAs can cause functional desensitization  
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20 of the  $\beta$ 2AR in mast cells. Regular use of both SABAs and LABAs increases sputum  
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22 inflammatory cells,<sup>27,28</sup> and is associated with increased AHR, especially to allergen.<sup>11,13,28-30</sup>  
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27 These pro-inflammatory effects might account for an enhanced EIB in patients using LABAs.  
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32 LABAs have been demonstrated to be useful for many patients whose symptoms are not  
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34 adequately controlled with conventional doses of ICS alone<sup>3,4</sup>. However, in this study, we  
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36 demonstrated that in clinically stable asthmatic children on ICS/LABA combination therapy,  
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38 the cessation of the LABA can reduce and in most cases abolish EIB. Therefore, if EIB can  
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40 still be demonstrated in children whose asthma is controlled with ICS/LABA combination  
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42 therapy, changing therapy to ICS monotherapy should be considered. Further research is  
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44 required to determine whether this applies to the general population or to a specific subgroup  
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## Figure Legends

Figure 1. Mean  $\pm$  SD % fall in FEV<sub>1</sub> after exercise challenge after combination therapy and after 3 weeks of treatment with ICS monotherapy.

Figure 2. Individual change in % fall in FEV<sub>1</sub> after exercise for those patients with a  $\geq 15\%$  fall in FEV<sub>1</sub> at the first exercise challenge.

Figure 3. Mean  $\pm$  SD % fall in FEV<sub>1</sub> after exercise challenge after combination therapy and after 3 weeks of treatment with ICS monotherapy for those children with a  $\geq 15\%$  fall in FEV<sub>1</sub> at the first exercise challenge.

Figure 4. Individual change in % fall in FEV<sub>1</sub> after exercise for those patients with a  $< 15\%$  fall in FEV<sub>1</sub> at the first exercise challenge.

Figure 5. Individual change in % fall in FEV<sub>1</sub> after exercise for those patients with a  $\geq 10\%$  fall in FEV<sub>1</sub> at the first exercise challenge.

Figure 6. Mean  $\pm$  SD % fall in FEV<sub>1</sub> after exercise challenge after combination therapy and after 3 weeks of treatment with ICS monotherapy for those children with a  $\geq 10\%$  fall in FEV<sub>1</sub> at the first exercise challenge.

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3 **Pilot study: The effect of reducing treatment on exercise induced bronchoconstriction.**  
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57 **Abbreviated Title:** Treatment reduction and EIB  
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Treatment reduction and EIB

**Abstract**

**Rationale:** Asthma therapy should be stepped up or stepped down in response to changes in asthma control. However, there is little evidence available on the optimal timing, sequence and degree of medication reductions. In this study we analyzed clinically stable asthmatic children who underwent a medication reduction from a combination preparation consisting of an inhaled corticosteroid (ICS) and long acting beta2-agonists (LABA) to monotherapy with the same dose of the ICS. We hypothesized that the extent of exercise induced bronchoconstriction (EIB) would not increase after the cessation of the LABA.

**Methods:** 19 children, aged 8-16 years, with clinically stable asthma, receiving LABA/ICS combination therapy, were analyzed in this open-label pilot study. Children performed an exercise challenge at baseline and 3 weeks after the medication reduction. Best values of spirometric measurements of the forced expiratory volume in 1 second (FEV<sub>1</sub>) were used for statistical calculations.

**Results:** Maximum percent fall in FEV<sub>1</sub> was significantly lower after 3 weeks of ICS monotherapy ( $p = 0.03$ ). 8/19 children had a  $\geq 15\%$  fall in FEV<sub>1</sub> after exercise at the initial exercise challenge. In this subgroup, maximum percent fall in FEV<sub>1</sub> after the medication reduction was significantly lower ( $p < 0.01$ ), and in 6 children it decreased to  $< 15\%$ , indicating they no longer had EIB.

**Conclusion:** In clinically stable asthmatic children on LABA/ICS combination therapy, the cessation of the LABA can reduce and in most cases abolish EIB.

**Keywords:** asthma, children, long acting bronchodilator agent, inhaled corticosteroid

## Introduction

According to international guidelines, asthma therapy should be stepped up or stepped down in response to changes in asthma control.<sup>1,2</sup> Combination therapy with an inhaled corticosteroid (ICS) and long acting beta2-agonist (LABA) is often prescribed as the third step in treatment regimens.<sup>1,2</sup> There are many arguments in favor of this combination.<sup>3</sup> A meta-analysis reviewing LABA treatment for childhood asthma concluded that the addition of a LABA to an ICS improved pulmonary function measures, reduced the use of rescue medications and improved quality of life measures.<sup>4</sup> LABAs are also effectively used as prophylaxis for exercise induced bronchoconstriction (EIB).<sup>5-7</sup> EIB occurs in the majority of asthmatic children and is an index of airway hyperresponsiveness (AHR). However, regular use of LABAs can lead to downregulation of the beta2-adrenoreceptor ( $\beta$ 2AR), resulting in the development of tolerance.<sup>8</sup> This implies that the duration of the bronchoprotective effect of a LABA against EIB is reduced.<sup>6,7,9,10</sup> Furthermore, the recovery time from EIB to pre-exercise lung function after rescue therapy with a short-acting beta2-agonist (SABA) is prolonged.<sup>11,12</sup> Regular treatment with SABAs can even enhance the severity of EIB.<sup>11,13</sup>

By reviewing the medical records of asthmatic adults, Yawn et al. found that only 13% of medication changes were step-down changes.<sup>14</sup> Reductions of the dosage were about twice as common as steps down in the class of medication prescribed. There is little evidence available on the optimal timing, sequence and degree of treatment reductions. When asthma is controlled with LABA/ICS combination therapy, the suggested step-down approach for adult asthmatics is to reduce the dose of the ICS.<sup>15-17</sup> An alternative is to discontinue the LABA and



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3 continue ICS monotherapy at the same dose.<sup>1,2</sup> The effect of stepping down treatment from  
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5 LABA/ICS combination therapy to ICS monotherapy on EIB has not yet been studied.  
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8 In this study, we analyzed this medication reduction in clinically stable asthmatic children.  
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10 Because the development of tolerance has an impact on the severity of EIB, we hypothesized  
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12 that the extent of EIB would not increase after the cessation of the LABA.  
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## Materials and Methods

### *Subjects*

Children were recruited from the outpatient clinic of the Medisch Spectrum Twente in Enschede. Fifty-two children with clinically stable asthma for > 3 months receiving treatment with LABA/ICS combination therapy, who underwent a medication reduction according to treatment guidelines<sup>1,2</sup>, were selected. Twenty-four otherwise healthy children, aged 8-16 years, with a history of allergy (confirmed by a positive RAST test on  $\geq 1$  allergen) and EIB (confirmed by a previous exercise challenge) were asked to participate in this study. Twenty children signed an informed consent form and were included in the study. Children had to be able to run on a treadmill and perform reproducible spirometry (i.e. variation of percentage of the predicted value in 3 of 5 consecutive measurements < 5%). Their forced expiratory volume in one second (FEV<sub>1</sub>) had to be at least 70% of predicted normal value. Children were required to withhold the use of leukotriene receptor antagonists (LTRAs), intranasal steroids, LABAs and ICSs for 24 hours and SABAs for 8 hours before both exercise challenges. No vigorous exercise was permitted for 4 hours before an exercise challenge.

### *Study Design*

This was an open-label pilot study. Children and their parents were contacted twice, four and two weeks prior to the first visit, to inform them about the importance of medication adherence. During the initial visit all children were asked to fill out Juniper's asthma control questionnaire (ACQ) and pediatric asthma quality of life questionnaire (PAQLQ). They performed an exercise challenge, with pulmonary function tests before and after the

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3 challenge, at the local ice rink, Euregio Kunstijsbaan, Enschede. Standard pulmonary function  
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5 test in this study consisted of a duplicated expiratory flow-volume loop.  
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8 After the initial visit treatment was reduced from LABA/ICS combination therapy to  
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10 monotherapy with the same dose of the ICS. The second visit was scheduled at the local ice  
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12 rink within 3 weeks after the first visit. During the second visit children were again asked to  
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14 fill out both questionnaires and performed a second exercise challenge. This study was  
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16 conducted with permission from the local Medical Ethics Committee.  
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### 19 20 21 22 *Questionnaires*

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24 The ACQ has 7 questions, scoring 5 symptoms, baseline FEV<sub>1</sub> % predicted and daily rescue  
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26 bronchodilator use. Children can respond to these questions on a 7-point scale (0 = no  
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28 impairment, 6 = maximum impairment). Baseline FEV<sub>1</sub> % predicted is also scored on a 7-  
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30 point scale. The questions are equally weighted and the ACQ score is the mean of the 7  
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32 questions and therefore between 0 (totally controlled) and 6 (severely uncontrolled).  
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36 The PAQLQ has 23 questions in 3 domains; symptoms, activity limitation and emotional  
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38 function. Children can respond on a 7-point scale (1 = maximum impairment, 7 = no  
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40 impairment). The total PAQLQ score is the mean of all 23 questions and therefore between 1  
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42 (impaired quality of life) and 7 (no impairment in quality of life). Domain scores are the  
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44 means of the items in those domains.  
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### 50 51 *Fraction of Exhaled Nitric Oxide*

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53 FE<sub>NO</sub> was measured before any forced expiratory maneuvers according to current guidelines<sup>18</sup>  
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55 at an exhaled flow rate of 50 ml/sec. The single-breath online measurement method was used  
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57 to measure FE<sub>NO</sub>. Children were asked to exhale to residual volume and then inhale gas with a  
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3 low NO concentration through a hand-held nitric oxide analyzer (Niox Mino<sup>®</sup>, Aerocrine,  
4 Stockholm, Sweden). Children inhaled to near to total lung capacity and immediately exhaled  
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6 at a constant flow rate.  
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### 10 11 12 *Pulmonary function test*

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14 A MicroLoop MK8 Spirometer (ML3535)<sup>®</sup>, with Spida5<sup>®</sup> software, was used to measure  
15 pulmonary volumes and flow-volume loops. The calibration of this spirometer was checked  
16 before testing. The expiratory flow-volume loop was recorded by instructing the children to  
17 perform a maximal expiratory effort from inspiratory vital capacity to residual volume. All  
18 measurements were performed in duplicate using a standard protocol.<sup>19</sup> Pulmonary function  
19 was calculated from the best curve.<sup>20</sup>  
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### 32 *Exercise challenge*

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34 Exercise challenge testing was performed by running with nose clipped on a treadmill  
35 (Reebok<sup>®</sup>, TR1 premium run) using the standardized ATS protocol.<sup>21</sup> A constant temperature  
36 of 10°C and absolute humidity of 4.2 g/kg (relative humidity of 56%) was obtained by testing  
37 in the local ice rink. Baseline spirometry was performed and the prechallenge FEV<sub>1</sub>  
38 documented as the best FEV<sub>1</sub> of two measurements. The test started with running at low  
39 speed on the treadmill with an incline of 10%. During the test, heart rate was continuously  
40 monitored by a radiographic device (Inventum SH 40<sup>®</sup>). The running speed of the treadmill  
41 was increased, raising the heart rate to approximately 90% of the predicted maximum ((220-  
42 age) x 0.9). This speed was maintained for six minutes. After the exercise challenge, flow  
43 volumes were measured at t = 1, 3, 6, 9, 12, 15 and 20 minutes. Maximum percent fall in  
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3 FEV<sub>1</sub> was used for further analysis. A fall of > 15% in FEV<sub>1</sub> from baseline was considered a  
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5 positive response.  
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### 10 *Statistical analysis*

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12 Best values of spirometric measurements of FEV<sub>1</sub> were used for statistical calculations with  
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14 SPSS<sup>®</sup> Statistics Version 17.0 for Windows<sup>®</sup>. Data were split into two groups: children with  
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16 EIB during the initial visit (defined as a > 15% fall in FEV<sub>1</sub> after exercise) and children  
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18 without EIB. Further calculations were performed on both groups separately and together.  
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21 The same analysis was performed on children with a > 10% fall in FEV<sub>1</sub> after the initial  
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23 exercise challenge.  
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27 Baseline percent predicted FEV<sub>1</sub> before both challenges were expressed as mean ± SD and  
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29 compared using Student's paired *t* test. Symptom scores on the ACQ and PAQLQ before both  
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31 challenges were compared using Wilcoxon's rank test. Maximum percent fall in FEV<sub>1</sub> after  
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33 both exercise challenges were compared using Student's paired *t* test.  
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36 Spearman's rank order correlation coefficient was calculated for the correlation between ACQ  
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38 and PAQLQ scores and % fall in FEV<sub>1</sub> after exercise.  
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## Results

Research population consisted of 20 children. One child was excluded from analysis because he was not able to perform reproducible spirometry. Data from 19 children were used for analysis (table 1). Among them were 13 boys and 6 girls. Mean age ( $\pm$  SD) was  $11.2 \pm 2.8$  years. Fifteen children were using the combination preparation fluticasone/salmeterol (median dose  $400\mu\text{g}$ ) before the first visit and stepped down to fluticasone monotherapy and 4 children were using the combination preparation budesonide/formoterol (median dose  $400\mu\text{g}$ ) before the first visit and stepped down to budesonide monotherapy. Six children were on a LTRA and six on an intranasal steroid.

Baseline  $\text{FEV}_1$  before the initial exercise challenge had a normal distribution with a mean ( $\pm$  SD) of  $94.1 \pm 13.6\%$  predicted value, which was not significantly different from baseline  $\text{FEV}_1$  three weeks after the medication reduction ( $94.6 \pm 15.1\%$  predicted value).

Mean maximum heart rate during the first exercise challenge was  $87.6 \pm 4.2\%$  of maximum heart rate, which was not significantly different from mean maximum heart rate during the second challenge ( $87.2 \pm 3.9\%$ ). SABA use was monitored by the asthma control questionnaire (question 6). Before the first exercise challenge (before LABAs were stopped) 8 children reported no SABA usage, 9 children reported the use of 1 - 2 puffs a few times per week and 2 children reported the use of 3 - 5 puffs (including pre-exercise use). After the medication reduction 8 children reported no SABA usage, 7 children reported the use of 1 - 2 puffs and 4 children reported the use of 3 - 5 puffs.

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3 Mean maximum percent fall in FEV<sub>1</sub> after the first exercise challenge was 14.5 ± 10.4%.

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5 Maximum percent fall in FEV<sub>1</sub> after the second exercise challenge was significantly lower (p  
6 = 0.03), with a mean of 9.0 ± 6.5%. (Fig 1) In 14 children the response to an exercise  
7 challenge, measured by the maximum percent fall in FEV<sub>1</sub>, decreased after the medication  
8 reduction. In 5 patients the response to an exercise challenge increased.  
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17 There were 8 children on LABA/ICS combination therapy that experienced EIB, defined by a  
18 ≥ 15% fall in FEV<sub>1</sub> after exercise. This subgroup had a mean maximum percent fall in FEV<sub>1</sub>  
19 after the first exercise challenge of 25.1 ± 6.2%. Maximum percent fall in FEV<sub>1</sub> after the  
20 second exercise challenge was significantly lower (p < 0.01), with a mean of 11.6 ± 8.1%.  
21 (Fig 2 and 3) In all 8 children, maximum percent fall in FEV<sub>1</sub> after exercise decreased after  
22 the medication reduction. In 6 children, maximum percent fall in FEV<sub>1</sub> was < 15%, indicating  
23 they were no longer experiencing EIB.  
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34 There were 11 children on LABA/ICS combination therapy without EIB (fall in FEV<sub>1</sub> <  
35 15%). In this subgroup, there was no change in mean maximum percent fall in FEV<sub>1</sub> after the  
36 medication reduction.(Fig 4) Only one child developed a mild EIB (fall in FEV<sub>1</sub> 17.1%) after  
37 the medication reduction. Analysis using a cutoff of ≥ 10% fall in FEV<sub>1</sub> provided similar  
38 statistically significant results.  
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48 At the initial visit asthma was generally well controlled with a median [range] score on the  
49 ACQ of 0.86 [3.00]. The children's quality of life was generally not impaired, with a total  
50 median [range] score on the PAQLQ at the initial visit of 5.8 [3.6] and a median score in the  
51 symptoms domain of 6.0 [2.7]. At the second visit median score on the ACQ was 0.71 [3.57],  
52 which was not significantly different from the initial score. Total and symptom scores on the  
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3 PAQLQ were respectively 6.3 [3.8] and 6.1 [3.7], which were not significantly different from  
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5 the initial scores.  
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8 There was a correlation between scores on the ACQ and PAQLQ (Spearman's rho = 0.43, p =  
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10 0.013). There was no correlation between scores on the ACQ or PAQLQ and maximum  
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12 percent fall in FEV<sub>1</sub> after exercise.  
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15 FE<sub>NO</sub> was measured at both visits in 14 patients. Mean ± SD was 16.6 ± 5.9 ppb after  
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17 LABA/ICS combination therapy and 15.6 ± 8.6 ppb after ICS monotherapy. This was not  
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19 significantly different.  
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## Discussion

In this study, we monitored a medication reduction from LABA/ICS combination therapy to monotherapy with the same dose of the ICS in clinically stable asthmatic children. Mean maximum percent fall in FEV<sub>1</sub> after an exercise challenge was significantly lower ( $p = 0.03$ ) after the medication change. In a subgroup of 8 children with a  $> 15\%$  fall in FEV<sub>1</sub> after the first exercise challenge, maximum percent fall in FEV<sub>1</sub> reduced in all children after the medication change ( $p < 0.01$ ). Of this subgroup, 6 children had a maximum percent fall in FEV<sub>1</sub>  $< 15\%$  after the second exercise challenge, indicating they were no longer experiencing EIB. This suggests that in asthmatic children on LABA/ICS combination therapy, the cessation of LABA can reduce and in most cases abolish EIB.

To our knowledge, the effect of reducing treatment from LABA/ICS combination therapy to ICS monotherapy on EIB has not yet been studied. According to international guidelines<sup>1,2</sup> treatment choices should be guided by asthma control. Once asthma control is achieved and maintained for at least 3 months, a step down can be considered. When asthma is controlled with LABA/ICS combination therapy, the suggested approach for adults is to reduce the ICS by approximately 25–50 percent every 3 months to the lowest dose possible.<sup>1,2</sup> An alternative is to discontinue the LABA and continue ICS monotherapy at the same dose.<sup>1,2</sup> Reducing the dose of the ICS is considered more effective than switching to an ICS alone.<sup>15-17</sup> The cessation of the LABA could result in a deterioration of asthma control, measured by morning peak expiratory flow (PEF), daily symptoms and bronchodilator use.<sup>15-17</sup> On the contrary, a report by Weinberger et al. describes an example of two adolescent patients whose EIB improved after the replacement of salmeterol with slow-release theophylline.<sup>22</sup>

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6 We analyzed the effect of stepping down treatment on EIB because EIB occurs in the majority  
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8 of asthmatic children and is considered to have a great impact on their quality of life<sup>23</sup>  
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10 (although we found no correlation between the extent of EIB and PAQLQ scores). Measuring  
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12 the airway response to exercise can be used as an indicator of AHR, which is indirectly  
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14 associated with airway inflammation. Titrating treatment guided by AHR leads to fewer  
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16 uncontrolled episodes in adults with asthma<sup>24</sup> and prevented a decline in lung function in  
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18 children with asthma.<sup>25</sup> This suggests that AHR is an indirect marker of asthma control.  
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24 A possible limitation of this study is the lack of a control group in whom we did not change  
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26 the medication regimen. In this pilot study, we decided to analyze regular medication  
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28 reductions, based on clinical decisions. However, the lack of a control group makes this study  
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30 susceptible to bias. The variability in fall in FEV<sub>1</sub> in standardized exercise challenges and  
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32 regression to the mean may have influenced our results. However, children included in this  
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34 study were clinically stable and their asthma was well controlled, as was confirmed by their  
35  
36 baseline lung function, low FE<sub>NO</sub> levels and ACQ scores. To exclude a learning bias, only  
37  
38 children who have performed an exercise challenge before were included. The consistent  
39  
40 decrease in fall in FEV<sub>1</sub> shown in children with EIB (Fig 2) cannot be solely contributed to  
41  
42 regression to the mean, neither can the mean decrease in maximum percent fall in FEV<sub>1</sub> from  
43  
44 25.1% to 11.6%. In an epidemiological study by Haby et al reproducibility of the % fall in  
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46 FEV<sub>1</sub> to a standardized exercise challenge was assessed by the calculation of the single  
47  
48 measurement 95% range. A 95% range of ± 12% was calculated, meaning that there is a 95%  
49  
50 probability that the true value for a subject is within the range of 12% fall in FEV<sub>1</sub> around the  
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52 single measurement value.<sup>26</sup>  
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3 Exercise challenge responses may be influenced by climatic and environmental factors such  
4 as circulating allergen. To exclude a seasonal bias, this study was performed outside the main  
5 pollen season. Second visits were planned  $21 \pm 6$  days after the first visit. There were no  
6 differences between baseline FEV<sub>1</sub> % predicted, FE<sub>NO</sub> levels and scores on the ACQ and  
7 PAQLQ before both challenges.  
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15 To optimize adherence, children and their parents were informed about its importance four  
16 weeks prior to the first exercise challenge and again by a telephonic contact two weeks prior  
17 to the first exercise challenge. At the first visit to the ice rink, they reported an adherence of  
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86  $\pm$  12%.

A reversal of the previously developed tolerance due to regular use of LABAs could explain  
the reduction in EIB when LABAs were discontinued. Regular use of LABAs leads to  
downregulation of the  $\beta$ 2AR,<sup>8</sup> resulting in a reduction of the duration of the bronchoprotective  
effect of a LABA against EIB<sup>6,7,9,10</sup> and a prolonged recovery time from EIB after rescue  
therapy with a SABA.<sup>11,12</sup> Although corticosteroids increase transcription of the  $\beta$ 2AR-gene,  
which could theoretically compensate for the downregulation of the  $\beta$ 2AR,<sup>3</sup> tolerance is not  
prevented by the concomitant use of ICSs.<sup>9,12,27,28</sup>

Regular use of SABAs or LABAs could paradoxically have a pro-inflammatory effect. In  
vitro, incubation of monocytes with increasing doses of terbutaline induced a shift of the  
human Th1-/Th2-type cytokine balance toward a Th2-type response.<sup>29</sup> Incubation of human  
mast cells with formoterol or salmeterol abolished the  $\beta$ 2AR-mediated inhibition of histamine  
release.<sup>30</sup> This indicates that regular exposure to LABAs can cause functional desensitization  
of the  $\beta$ 2AR in mast cells. Regular use of both SABAs and LABAs increases sputum

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3 inflammatory cells,<sup>31,32</sup> and is associated with increased AHR, especially to allergen.<sup>11,13,32-34</sup>

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5 These pro-inflammatory effects might account for an enhanced EIB in patients using LABAs.

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10 LABAs have been demonstrated to be useful for many patients whose symptoms are not  
11  
12 adequately controlled with conventional doses of ICS alone<sup>3,4</sup>. However, in this pilot study,  
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14 we demonstrated that in clinically stable asthmatic children on LABA/ICS combination  
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16 therapy, the cessation of the LABA can reduce and in most cases abolish EIB. Therefore, if  
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18 EIB can still be demonstrated in children whose asthma is controlled with LABA/ICS  
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20 combination therapy, changing therapy to ICS monotherapy should be considered. Further  
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22 research is required to determine whether this applies to the general population or to a specific  
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24 subgroup of patients.  
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## Figure Legends

Figure 1. Mean  $\pm$  SD % fall in FEV<sub>1</sub> after exercise challenge after combination therapy and after 3 weeks of treatment with ICS monotherapy.

Figure 2. Individual change in % fall in FEV<sub>1</sub> after exercise for those patients with a  $\geq 15\%$  fall in FEV<sub>1</sub> at the first exercise challenge.

Figure 3. Mean  $\pm$  SD % fall in FEV<sub>1</sub> after exercise challenge after combination therapy and after 3 weeks of treatment with ICS monotherapy for those children with a  $\geq 15\%$  fall in FEV<sub>1</sub> at the first exercise challenge.

Figure 4. Individual change in % fall in FEV<sub>1</sub> after exercise for those patients with a  $< 15\%$  fall in FEV<sub>1</sub> at the first exercise challenge.

Figure 5. FEV<sub>1</sub> changes after exercise and after 100  $\mu$ g Salbutamol.

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2 **Pilot study: The effect of reducing treatment on exercise induced bronchoconstriction.**  
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47 **Abbreviated Title:** Treatment reduction and EIB  
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**Abstract**

**Rationale:** Asthma therapy should be stepped up or stepped down in response to changes in asthma control. However, there is little evidence available on the optimal timing, sequence and degree of medication reductions. In this study we analyzed clinically stable asthmatic children who underwent a medication reduction from a combination preparation consisting of an inhaled corticosteroid (ICS) and long acting beta2-agonist (LABA) to monotherapy with the same dose of the ICS. We hypothesized that the extent of exercise induced bronchoconstriction (EIB) would not increase after the cessation of the LABA.

**Methods:** 19 children, aged 8-16 years, with clinically stable asthma, receiving LABA/ICS combination therapy, were analyzed in this open-label pilot study. Children performed an exercise challenge at baseline and 3 weeks after the medication reduction. Best values of spirometric measurements of the forced expiratory volume in 1 second (FEV<sub>1</sub>) were used for statistical calculations.

**Results:** Maximum percent fall in FEV<sub>1</sub> was significantly lower after 3 weeks of ICS monotherapy ( $p = 0.03$ ). 8/19 children had a  $\geq 15\%$  fall in FEV<sub>1</sub> after exercise at the initial exercise challenge. In this subgroup, maximum percent fall in FEV<sub>1</sub> after the medication reduction was significantly lower ( $p < 0.01$ ), and in 6 children it decreased to  $< 15\%$ , indicating they no longer had EIB.

**Conclusion:** In clinically stable asthmatic children on LABA/ICS combination therapy, the cessation of the LABA can reduce and in most cases abolish EIB.

**Keywords:** asthma, children, long acting bronchodilator agent, inhaled corticosteroid

Treatment reduction and EIB

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## Introduction

According to international guidelines, asthma therapy should be stepped up or stepped down in response to changes in asthma control.<sup>1,2</sup> Combination therapy with an inhaled corticosteroid (ICS) and long acting beta2-agonist (LABA) is often prescribed as the third step in treatment regimens.<sup>1,2</sup> There are many arguments in favor of this combination.<sup>3</sup> A meta-analysis reviewing LABA treatment for childhood asthma concluded that the addition of a LABA to an ICS improved pulmonary function measures, reduced the use of rescue medications and improved quality of life measures.<sup>4</sup> LABAs are also effectively used as prophylaxis for exercise induced bronchoconstriction (EIB).<sup>5-7</sup> EIB occurs in the majority of asthmatic children and is an index of airway hyperresponsiveness (AHR). However, regular use of LABAs can lead to downregulation of the beta2-adrenoreceptor ( $\beta$ 2AR), resulting in the development of tolerance.<sup>8</sup> This implies that the duration of the bronchoprotective effect of a LABA against EIB is reduced.<sup>6,7,9,10</sup> Furthermore, the recovery time from EIB to pre-exercise lung function after rescue therapy with a short-acting beta2-agonist (SABA) is prolonged.<sup>11,12</sup> Regular treatment with SABAs can even enhance the severity of EIB.<sup>11,13</sup>

By reviewing the medical records of asthmatic adults, Yawn et al. found that only 13% of medication changes were step-down changes.<sup>14</sup> Reductions of the dosage were about twice as common as steps down in the class of medication prescribed. There is little evidence available on the optimal timing, sequence and degree of treatment reductions. When asthma is controlled with LABA/ICS combination therapy, the suggested step-down approach for adult asthmatics is to reduce the dose of the ICS.<sup>15-17</sup> An alternative that is recommended by the FDA<sup>18</sup> is to discontinue the LABA and continue ICS monotherapy at the same dose.<sup>1,2</sup> The

1  
2 effect of stepping down treatment from LABA/ICS combination therapy to ICS monotherapy  
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4 on EIB has not yet been studied.

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6 In this study, we analyzed this medication reduction in clinically stable asthmatic children.

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8 Because the development of tolerance has an impact on the severity of EIB, we hypothesized  
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10 that the extent of EIB would not increase after the cessation of the LABA.  
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51 Treatment reduction and EIB

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## Materials and Methods

### *Subjects*

Children were recruited from the outpatient clinic of the Medisch Spectrum Twente in Enschede. Fifty-two children with clinically stable asthma for > 3 months receiving treatment with LABA/ICS combination therapy, who underwent a medication reduction according to treatment guidelines<sup>1,2</sup>, were selected. Twenty-four otherwise healthy children, aged 8-16 years, with a history of allergy (confirmed by a positive RAST test on  $\geq 1$  allergen) and EIB (confirmed by a previous exercise challenge) were asked to participate in this study. Twenty children signed an informed consent form and were included in the study. Children had to be able to run on a treadmill and perform reproducible spirometry (i.e. variation of percentage of the predicted value in 3 of 5 consecutive measurements < 5%). Their forced expiratory volume in one second (FEV<sub>1</sub>) had to be at least 70% of predicted normal value. Children were required to withhold the use of leukotriene receptor antagonists (LTRAs), intranasal steroids, LABAs and ICSs for 24 hours and SABAs for 8 hours before both exercise challenges. No vigorous exercise was permitted for 4 hours before an exercise challenge.

### *Study Design*

This was an open-label pilot study. Children and their parents were contacted twice, four and two weeks prior to the first visit, to inform them about the importance of medication adherence. During the initial visit all children were asked to fill out Juniper's asthma control questionnaire (ACQ) and pediatric asthma quality of life questionnaire (PAQLQ). They performed an exercise challenge, with pulmonary function tests before and after the

Treatment reduction and EIB

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1  
2 challenge, at the local ice rink, Euregio Kunstijsbaan, Enschede. Standard pulmonary function  
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4 test in this study consisted of a duplicated expiratory flow-volume loop.

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6 After the initial visit treatment was reduced from LABA/ICS combination therapy to  
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8 monotherapy with the same dose of the ICS. The second visit was scheduled at the local ice  
9  
10 rink, 3 weeks after the first visit. During the second visit children were again asked to fill out  
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12 both questionnaires and performed a second exercise challenge. This study was conducted  
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14 with permission from the local Medical Ethics Committee.

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### 17 18 *Questionnaires*

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20 The ACQ has 7 questions, scoring 5 symptoms, baseline FEV<sub>1</sub> % predicted and daily rescue  
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22 bronchodilator use. Children can respond to these questions on a 7-point scale (0 = no  
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24 impairment, 6 = maximum impairment). Baseline FEV<sub>1</sub> % predicted is also scored on a 7-  
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26 point scale. The questions are equally weighted and the ACQ score is the mean of the 7  
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28 questions and therefore between 0 (totally controlled) and 6 (severely uncontrolled).

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30 The PAQLQ has 23 questions in 3 domains; symptoms, activity limitation and emotional  
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32 function. Children can respond on a 7-point scale (1 = maximum impairment, 7 = no  
33  
34 impairment). The total PAQLQ score is the mean of all 23 questions and therefore between 1  
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36 (impaired quality of life) and 7 (no impairment in quality of life). Domain scores are the  
37  
38 means of the items in those domains.

### 39 40 41 *Fraction of Exhaled Nitric Oxide*

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43 FE<sub>NO</sub> was measured before any forced expiratory maneuvers according to current guidelines<sup>19</sup>  
44  
45 at an exhaled flow rate of 50 ml/sec. The single-breath online measurement method was used  
46  
47 to measure FE<sub>NO</sub>. Children were asked to exhale to residual volume and then inhale gas with a  
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51 Treatment reduction and EIB

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1  
2 low NO concentration through a hand-held nitric oxide analyzer (Niox Mino<sup>®</sup>, Aerocrine,  
3 Stockholm, Sweden). Children inhaled to near to total lung capacity and immediately exhaled  
4 at a constant flow rate.  
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### 9 10 *Pulmonary function test*

11 A MicroLoop MK8 Spirometer (ML3535)<sup>®</sup>, with Spida5<sup>®</sup> software, was used to measure  
12 pulmonary volumes and flow-volume loops. The calibration of this spirometer was checked  
13 before testing. The expiratory flow-volume loop was recorded by instructing the children to  
14 perform a maximal expiratory effort from inspiratory vital capacity to residual volume. All  
15 measurements were performed in duplicate using a standard protocol.<sup>20</sup> Pulmonary function  
16 was calculated from the best curve.<sup>21</sup>  
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### 26 *Exercise challenge*

27 Exercise challenge testing was performed by running with nose clipped on a treadmill  
28 (Reebok<sup>®</sup>, TR1 premium run) using the standardized ATS protocol.<sup>22</sup> A constant temperature  
29 of 10°C and absolute humidity of 4.2 g/kg (relative humidity of 56%) was obtained by testing  
30 in the local ice rink. Baseline spirometry was performed and the prechallenge FEV<sub>1</sub>  
31 documented as the best FEV<sub>1</sub> of two measurements. The test started with running at low  
32 speed on the treadmill with an incline of 10%. During the test, heart rate was continuously  
33 monitored by a radiographic device (Inventum SH 40<sup>®</sup>). The running speed of the treadmill  
34 was increased, raising the heart rate to approximately 90% of the predicted maximum ((220-  
35 age) x 0.9). This speed was maintained for six minutes. After the exercise challenge, flow  
36 volumes were measured at t = 1, 3, 6, 9, 12, 15 and 20 minutes. Maximum percent fall in  
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2 FEV<sub>1</sub> was used for further analysis. A fall of  $\geq 15\%$  in FEV<sub>1</sub> from baseline was considered a  
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4 positive response.

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### 8 *Statistical analysis*

10 Best values of spirometric measurements of FEV<sub>1</sub> were used for statistical calculations with  
11 SPSS® Statistics Version 17.0 for Windows®. Data were split into two groups: children with  
12 EIB during the initial visit (defined as a  $\geq 15\%$  fall in FEV<sub>1</sub> after exercise) and children  
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14 without EIB. Further calculations were performed on both groups separately and together.

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17 The same analysis was performed on children with a  $\geq 10\%$  fall in FEV<sub>1</sub> after the initial  
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19 exercise challenge.

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21 Baseline percent predicted FEV<sub>1</sub> before both challenges were expressed as mean  $\pm$  SD and  
22 compared using Student's paired *t* test. Symptom scores on the ACQ and PAQLQ before both  
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24 challenges were compared using Wilcoxon's rank test. Maximum percent fall in FEV<sub>1</sub> after  
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26 both exercise challenges were compared using Student's paired *t* test.

29 Spearman's rank order correlation coefficient was calculated for the correlation between ACQ  
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31 and PAQLQ scores and % fall in FEV<sub>1</sub> after exercise.

## Results

Research population consisted of 20 children. One child was excluded from analysis because he was not able to perform reproducible spirometry. Data from 19 children were used for analysis (table 1). Among them were 13 boys and 6 girls. Mean age ( $\pm$  SD) was  $11.2 \pm 2.8$  years. Fifteen children were using the combination preparation fluticasone/salmeterol (median dose  $400\mu\text{g}$ ) before the first visit and stepped down to fluticasone monotherapy and 4 children were using the combination preparation budesonide/formoterol (median dose  $400\mu\text{g}$ ) before the first visit and stepped down to budesonide monotherapy. Six children were on a LTRA and six on an intranasal steroid.

Baseline FEV<sub>1</sub> before the initial exercise challenge had a normal distribution with a mean ( $\pm$  SD) of  $94.1 \pm 13.6\%$  predicted value, which was not significantly different from baseline FEV<sub>1</sub> three weeks after the medication reduction ( $94.6 \pm 15.1\%$  predicted value).

Mean maximum heart rate during the first exercise challenge was  $87.6 \pm 4.2\%$  of maximum heart rate, which was not significantly different from mean maximum heart rate during the second challenge ( $87.2 \pm 3.9\%$ ). SABA use was monitored by the asthma control

questionnaire (question 6). Before the first exercise challenge (before LABAs were stopped) children reported an average use of 3.4 puffs of SABA per week (including pre-exercise use).

After the medication reduction children reported an average use of 4.2 puffs per week.

Mean maximum percent fall in FEV<sub>1</sub> after the first exercise challenge was  $14.5 \pm 10.4\%$ .

Maximum percent fall in FEV<sub>1</sub> after the second exercise challenge was significantly lower ( $p = 0.03$ ), with a mean of  $9.0 \pm 6.5\%$ . (Fig 1 and 5) In 14 children the response to an exercise

**Deleted:** 8 children reported no SABA usage, 9 children reported the use of 1 - 2 puffs per week and 2 children reported the use of 3 - 5 puffs (including pre-exercise use). After the medication reduction 8 children reported no SABA usage, 7 children reported the use of 1 - 2 puffs and 4 children reported the use of 3 - 5 puffs.

Treatment reduction and EIB

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2 challenge, measured by the maximum percent fall in FEV<sub>1</sub>, decreased after the medication  
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4 reduction. In 5 children the response to an exercise challenge increased.

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8 There were 8 children on LABA/ICS combination therapy that experienced EIB, defined by a  
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10  $\geq 15\%$  fall in FEV<sub>1</sub> after exercise. This subgroup had a mean maximum percent fall in FEV<sub>1</sub>  
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12 after the first exercise challenge of  $25.1 \pm 6.2\%$ . Maximum percent fall in FEV<sub>1</sub> after the  
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14 second exercise challenge was significantly lower ( $p < 0.01$ ), with a mean of  $11.6 \pm 8.1\%$ .  
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16 (Fig 2 and 3) In all 8 children, maximum percent fall in FEV<sub>1</sub> after exercise decreased after  
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18 the medication reduction. In 6 children, maximum percent fall in FEV<sub>1</sub> was  $< 15\%$ , indicating  
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20 they were no longer experiencing EIB.

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22 There were 11 children on LABA/ICS combination therapy without EIB (fall in FEV<sub>1</sub>  $<$   
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24  $15\%$ ). In this subgroup, there was no change in mean maximum percent fall in FEV<sub>1</sub> after the  
25  
26 medication reduction.(Fig 4) Only one child developed a mild EIB (fall in FEV<sub>1</sub>  $17.1\%$ ) after  
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28 the medication reduction. Analysis using a cutoff of  $\geq 10\%$  fall in FEV<sub>1</sub> provided similar  
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30 statistically significant results.

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33 At the initial visit asthma was generally well controlled with a median [range] score on the  
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35 ACQ of 0.86 [3.00]. The children's quality of life was generally not impaired, with a total  
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37 median [range] score on the PAQLQ at the initial visit of 5.8 [3.6] and a median score in the  
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39 symptoms domain of 6.0 [2.7]. At the second visit median score on the ACQ was 0.71 [3.57],  
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41 which was not significantly different from the initial score. Total and symptom scores on the  
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43 PAQLQ were respectively 6.3 [3.8] and 6.1 [3.7], which were not significantly different from  
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45 the initial scores.

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2 There was a correlation between scores on the ACQ and PAQLQ (Spearman's rho = 0.43, p =  
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4 0.013). There was no correlation between scores on the ACQ or PAQLQ and maximum  
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6 percent fall in FEV<sub>1</sub> after exercise.  
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8 FE<sub>NO</sub> was measured at both visits in 14 patients. Mean ± SD was 16.6 ± 5.9 ppb after  
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10 LABA/ICS combination therapy and 15.6 ± 8.6 ppb after ICS monotherapy. This was not  
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12 significantly different.  
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## Discussion

In this study, we monitored a medication reduction from LABA/ICS combination therapy to monotherapy with the same dose of the ICS in clinically stable asthmatic children. Mean maximum percent fall in FEV<sub>1</sub> after an exercise challenge was significantly lower ( $p = 0.03$ ) after the medication change. In a subgroup of 8 children with a  $\geq 15\%$  fall in FEV<sub>1</sub> after the first exercise challenge, maximum percent fall in FEV<sub>1</sub> reduced in all children after the medication change ( $p < 0.01$ ). Of this subgroup, 6 children had a maximum percent fall in FEV<sub>1</sub>  $< 15\%$  after the second exercise challenge, indicating they were no longer experiencing EIB. This suggests that in asthmatic children on LABA/ICS combination therapy, the cessation of LABA can reduce and in most cases abolish EIB.

To our knowledge, the effect of reducing treatment from LABA/ICS combination therapy to ICS monotherapy on EIB has not yet been studied. According to international guidelines<sup>1,2</sup> treatment choices should be guided by asthma control. Once asthma control is achieved and maintained for at least 3 months, a step down can be considered. When asthma is controlled with LABA/ICS combination therapy, the suggested approach for adults is to reduce the ICS by approximately 25–50 percent every 3 months to the lowest dose possible.<sup>1,2</sup> An alternative that was recently recommended by the FDA<sup>18</sup> is to discontinue the LABA and continue ICS monotherapy at the same dose.<sup>1,2</sup> In adults, reducing the dose of the ICS is considered more effective than switching to an ICS alone.<sup>15-17</sup> The cessation of the LABA could result in a deterioration of asthma control.<sup>15-17</sup> However, the benefits shown in these studies were largely a measure of the beta-agonist effect, such as improved peak expiratory flow and reduced rescue use of SABAs. On the contrary, a report by Weinberger et al. describes an example of

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2 two adolescent patients whose EIB improved after the replacement of salmeterol with slow-  
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4 release theophylline.<sup>23</sup>  
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8 We analyzed the effect of stepping down treatment on EIB because EIB occurs in the majority  
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10 of asthmatic children and is considered to have a great impact on their quality of life<sup>24</sup>  
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12 (although we found no correlation between the extent of EIB and PAQLQ scores). Measuring  
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14 the airway response to exercise can be used as an indicator of AHR, which is indirectly  
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16 associated with airway inflammation. Titrating treatment guided by AHR leads to fewer  
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18 uncontrolled episodes in adults with asthma<sup>25</sup> and prevented a decline in lung function in  
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20 children with asthma.<sup>26</sup> This suggests that AHR is an indirect marker of asthma control.  
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24 A possible limitation of this study is the lack of a control group in whom we did not change  
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26 the medication regimen. In this pilot study, we decided to analyze regular medication  
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28 reductions, based on clinical decisions. However, the lack of a control group makes this study  
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30 susceptible to bias. The variability in fall in FEV<sub>1</sub> in standardized exercise challenges and  
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32 regression to the mean may have influenced our results. However, children included in this  
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34 study were clinically stable and their asthma was well controlled, as was confirmed by their  
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36 baseline lung function, low FE<sub>NO</sub> levels and ACQ scores. To exclude a learning bias, only  
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38 children who have performed an exercise challenge before were included. The consistent  
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40 decrease in fall in FEV<sub>1</sub> shown in children with EIB (Fig 2) cannot be solely contributed to  
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42 regression to the mean, neither can the mean decrease in maximum percent fall in FEV<sub>1</sub> from  
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44 25.1% to 11.6 %. In an epidemiological study by Haby et al reproducibility of the % fall in  
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46 FEV<sub>1</sub> to a standardized exercise challenge was assessed by the calculation of the single  
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48 measurement 95% range. A 95% range of  $\pm 12\%$  was calculated, meaning that there is a 95%  
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probability that the true value for a subject is within the range of 12% fall in FEV<sub>1</sub> around the single measurement value.<sup>27</sup>

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Exercise challenge responses may be influenced by climatic and environmental factors such as circulating allergen. To exclude a seasonal bias, this study was performed outside the main pollen season. Second visits were planned 3 weeks after the first visit. There were no differences between baseline FEV<sub>1</sub> % predicted, FE<sub>NO</sub> levels and scores on the ACQ and PAQLQ before both challenges.

To optimize adherence, children and their parents were informed about its importance four weeks prior to the first exercise challenge and again by a telephonic contact two weeks prior to the first exercise challenge. At the first visit to the ice rink, they reported an adherence of 86 ± 12%.

A reversal of the previously developed tolerance due to regular use of LABAs could explain the reduction in EIB when LABAs were discontinued. Regular use of LABAs leads to downregulation of the β2AR.<sup>8</sup> This results in a reduction of the duration of the bronchoprotective effect of a LABA against EIB<sup>6,7,9,10</sup> and a prolonged recovery time from EIB after rescue therapy with a SABA.<sup>11,12</sup> Although corticosteroids increase transcription of the β2AR-gene, which could theoretically compensate for the downregulation of the β2AR,<sup>3</sup> tolerance is not prevented by the concomitant use of ICSs.<sup>9,12,28-30</sup>

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In addition to the development of tolerance to the bronchoprotective and bronchodilative effects, a growing body of evidence supports the hypothesis that regular use of beta2-agonists could increase AHR, especially to allergen.<sup>11,13,31-33</sup> The increase in sputum inflammatory cells<sup>31,34</sup> after regular use of beta2-agonists suggests they could paradoxically have a pro-inflammatory effect. Regular exposure to LABAs can cause functional desensitization of the

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Treatment reduction and EIB

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2  $\beta$ 2AR in mast cells<sup>35</sup> and airway smooth muscle<sup>36</sup> (ref) The complex signaling pathway underlying  
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4 the relationship between AHR and the  $\beta$ 2AR is still being explored. There appears to be a  
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6 differentiation between downregulation of the  $\beta$ 2AR (causing less effective bronchodilatation) and  
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8 enhanced contractile signaling (causing enhanced AHR) due to chronic activation of the  $\beta$ 2AR.<sup>37</sup> Both  
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10 occur with regular use of beta2-agonists.

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Deleted: Regular use of both SABAs and LABAs increases sputum inflammatory cells,<sup>31,32</sup> and is associated with increased AHR, especially to allergen.<sup>11,13,32-34</sup> These pro-inflammatory effects might account for an enhanced EIB in patients using LABAs.

13 LABAs have been demonstrated to be useful for many patients whose symptoms are not  
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15 adequately controlled with conventional doses of ICS alone<sup>3,4</sup>. However, in this pilot study,  
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17 we demonstrated that in clinically stable asthmatic children on LABA/ICS combination  
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19 therapy, the cessation of the LABA can reduce and in most cases abolish EIB. Therefore, if  
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21 EIB can still be demonstrated in children whose asthma is controlled with LABA/ICS  
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23 combination therapy, changing therapy to ICS monotherapy should be considered. Further  
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25 research is required to determine whether this applies to the general population or to a specific  
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**Figure Legends**

Figure 1. Mean  $\pm$  SD % fall in FEV<sub>1</sub> after exercise challenge after combination therapy and after 3 weeks of treatment with ICS monotherapy.

Figure 2. Individual change in % fall in FEV<sub>1</sub> after exercise for those patients with a  $\geq$  15% fall in FEV<sub>1</sub> at the first exercise challenge.

Figure 3. Mean  $\pm$  SD % fall in FEV<sub>1</sub> after exercise challenge after combination therapy and after 3 weeks of treatment with ICS monotherapy for those children with a  $\geq$  15% fall in FEV<sub>1</sub> at the first exercise challenge.

Figure 4. Individual change in % fall in FEV<sub>1</sub> after exercise for those patients with a  $<$  15% fall in FEV<sub>1</sub> at the first exercise challenge.

Figure 5. FEV<sub>1</sub> changes after exercise and after 100  $\mu$ g Salbutamol.

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3 **Pilot study: The effect of reducing treatment on exercise induced bronchoconstriction.**  
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57 **Abbreviated Title:** Treatment reduction and EIB  
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Treatment reduction and EIB

## Abstract

**Rationale:** Asthma therapy should be stepped up or stepped down in response to changes in asthma control. However, there is little evidence available on the optimal timing, sequence and degree of medication reductions. In this study we analyzed clinically stable asthmatic children who underwent a medication reduction from a combination preparation consisting of an inhaled corticosteroid (ICS) and long acting beta2-agonist (LABA) to monotherapy with the same dose of the ICS. We hypothesized that the extent of exercise induced bronchoconstriction (EIB) would not increase after the cessation of the LABA.

**Methods:** 19 children, aged 8-16 years, with clinically stable asthma, receiving LABA/ICS combination therapy, were analyzed in this open-label pilot study. Children performed an exercise challenge at baseline and 3 weeks after the medication reduction. Best values of spirometric measurements of the forced expiratory volume in 1 second (FEV<sub>1</sub>) were used for statistical calculations.

**Results:** Maximum percent fall in FEV<sub>1</sub> was significantly lower after 3 weeks of ICS monotherapy ( $p = 0.03$ ). 8/19 children had a  $\geq 15\%$  fall in FEV<sub>1</sub> after exercise at the initial exercise challenge. In this subgroup, maximum percent fall in FEV<sub>1</sub> after the medication reduction was significantly lower ( $p < 0.01$ ), and in 6 children it decreased to  $< 15\%$ , indicating they no longer had EIB.

**Conclusion:** In clinically stable asthmatic children on LABA/ICS combination therapy, the cessation of the LABA can reduce and in most cases abolish EIB.

**Keywords:** asthma, children, long acting bronchodilator agent, inhaled corticosteroid



## Introduction

According to international guidelines, asthma therapy should be stepped up or stepped down in response to changes in asthma control.<sup>1,2</sup> Combination therapy with an inhaled corticosteroid (ICS) and long acting beta2-agonist (LABA) is often prescribed as the third step in treatment regimens.<sup>1,2</sup> There are many arguments in favor of this combination.<sup>3</sup> A meta-analysis reviewing LABA treatment for childhood asthma concluded that the addition of a LABA to an ICS improved pulmonary function measures, reduced the use of rescue medications and improved quality of life measures.<sup>4</sup> LABAs are also effectively used as prophylaxis for exercise induced bronchoconstriction (EIB).<sup>5-7</sup> EIB occurs in the majority of asthmatic children and is an index of airway hyperresponsiveness (AHR). However, regular use of LABAs can lead to downregulation of the beta2-adrenoreceptor ( $\beta$ 2AR), resulting in the development of tolerance.<sup>8</sup> This implies that the duration of the bronchoprotective effect of a LABA against EIB is reduced.<sup>6,7,9,10</sup> Furthermore, the recovery time from EIB to pre-exercise lung function after rescue therapy with a short-acting beta2-agonist (SABA) is prolonged.<sup>11,12</sup> Regular treatment with SABAs can even enhance the severity of EIB.<sup>11,13</sup>

By reviewing the medical records of asthmatic adults, Yawn et al. found that only 13% of medication changes were step-down changes.<sup>14</sup> Reductions of the dosage were about twice as common as steps down in the class of medication prescribed. There is little evidence available on the optimal timing, sequence and degree of treatment reductions. When asthma is controlled with LABA/ICS combination therapy, the suggested step-down approach for adult asthmatics is to reduce the dose of the ICS.<sup>15-17</sup> An alternative that is recommended by the FDA<sup>18</sup> is to discontinue the LABA and continue ICS monotherapy at the same dose.<sup>1,2</sup> The

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3 effect of stepping down treatment from LABA/ICS combination therapy to ICS monotherapy  
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5 on EIB has not yet been studied.  
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8 In this study, we analyzed this medication reduction in clinically stable asthmatic children.  
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10 Because the development of tolerance has an impact on the severity of EIB, we hypothesized  
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12 that the extent of EIB would not increase after the cessation of the LABA.  
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For Peer Review

## Materials and Methods

### *Subjects*

Children were recruited from the outpatient clinic of the Medisch Spectrum Twente in Enschede. Fifty-two children with clinically stable asthma for > 3 months receiving treatment with LABA/ICS combination therapy, who underwent a medication reduction according to treatment guidelines<sup>1,2</sup>, were selected. Twenty-four otherwise healthy children, aged 8-16 years, with a history of allergy (confirmed by a positive RAST test on  $\geq 1$  allergen) and EIB (confirmed by a previous exercise challenge) were asked to participate in this study. Twenty children signed an informed consent form and were included in the study. Children had to be able to run on a treadmill and perform reproducible spirometry (i.e. variation of percentage of the predicted value in 3 of 5 consecutive measurements < 5%). Their forced expiratory volume in one second (FEV<sub>1</sub>) had to be at least 70% of predicted normal value. Children were required to withhold the use of leukotriene receptor antagonists (LTRAs), intranasal steroids, LABAs and ICSs for 24 hours and SABAs for 8 hours before both exercise challenges. No vigorous exercise was permitted for 4 hours before an exercise challenge.

### *Study Design*

This was an open-label pilot study. Children and their parents were contacted twice, four and two weeks prior to the first visit, to inform them about the importance of medication adherence. During the initial visit all children were asked to fill out Juniper's asthma control questionnaire (ACQ) and pediatric asthma quality of life questionnaire (PAQLQ). They performed an exercise challenge, with pulmonary function tests before and after the

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3 challenge, at the local ice rink, Euregio Kunstijsbaan, Enschede. Standard pulmonary function  
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5 test in this study consisted of a duplicated expiratory flow-volume loop.  
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8 After the initial visit treatment was reduced from LABA/ICS combination therapy to  
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10 monotherapy with the same dose of the ICS. The second visit was scheduled at the local ice  
11  
12 rink 3 weeks after the first visit. During the second visit children were again asked to fill out  
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14 both questionnaires and performed a second exercise challenge. This study was conducted  
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16 with permission from the local Medical Ethics Committee.  
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### 20 21 22 *Questionnaires*

23  
24 The ACQ has 7 questions, scoring 5 symptoms, baseline FEV<sub>1</sub> % predicted and daily rescue  
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26 bronchodilator use. Children can respond to these questions on a 7-point scale (0 = no  
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28 impairment, 6 = maximum impairment). Baseline FEV<sub>1</sub> % predicted is also scored on a 7-  
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30 point scale. The questions are equally weighted and the ACQ score is the mean of the 7  
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32 questions and therefore between 0 (totally controlled) and 6 (severely uncontrolled).  
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36 The PAQLQ has 23 questions in 3 domains; symptoms, activity limitation and emotional  
37  
38 function. Children can respond on a 7-point scale (1 = maximum impairment, 7 = no  
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40 impairment). The total PAQLQ score is the mean of all 23 questions and therefore between 1  
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42 (impaired quality of life) and 7 (no impairment in quality of life). Domain scores are the  
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44 means of the items in those domains.  
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### 50 51 *Fraction of Exhaled Nitric Oxide*

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53 FE<sub>NO</sub> was measured before any forced expiratory maneuvers according to current guidelines<sup>19</sup>  
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55 at an exhaled flow rate of 50 ml/sec. The single-breath online measurement method was used  
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57 to measure FE<sub>NO</sub>. Children were asked to exhale to residual volume and then inhale gas with a  
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3 low NO concentration through a hand-held nitric oxide analyzer (Niox Mino<sup>®</sup>, Aerocrine,  
4 Stockholm, Sweden). Children inhaled to near to total lung capacity and immediately exhaled  
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6 at a constant flow rate.  
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### 9 10 11 12 *Pulmonary function test*

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14 A MicroLoop MK8 Spirometer (ML3535)<sup>®</sup>, with Spida5<sup>®</sup> software, was used to measure  
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16 pulmonary volumes and flow-volume loops. The calibration of this spirometer was checked  
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18 before testing. The expiratory flow-volume loop was recorded by instructing the children to  
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20 perform a maximal expiratory effort from inspiratory vital capacity to residual volume. All  
21  
22 measurements were performed in duplicate using a standard protocol.<sup>20</sup> Pulmonary function  
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24 was calculated from the best curve.<sup>21</sup>  
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### 32 *Exercise challenge*

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34 Exercise challenge testing was performed by running with nose clipped on a treadmill  
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36 (Reebok<sup>®</sup>, TR1 premium run) using the standardized ATS protocol.<sup>22</sup> A constant temperature  
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38 of 10°C and absolute humidity of 4.2 g/kg (relative humidity of 56%) was obtained by testing  
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40 in the local ice rink. Baseline spirometry was performed and the pre-challenge FEV<sub>1</sub>  
41  
42 documented as the best FEV<sub>1</sub> of two measurements. The test started with running at low  
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44 speed on the treadmill with an incline of 10%. During the test, heart rate was continuously  
45  
46 monitored by a radiographic device (Inventum SH 40<sup>®</sup>). The running speed of the treadmill  
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48 was increased, raising the heart rate to approximately 90% of the predicted maximum ((220-  
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50 age) x 0.9). This speed was maintained for six minutes. After the exercise challenge, flow  
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52 volumes were measured at t = 1, 3, 6, 9, 12, 15 and 20 minutes. Maximum percent fall in  
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3 FEV<sub>1</sub> was used for further analysis. A fall of  $\geq 15\%$  in FEV<sub>1</sub> from baseline was considered a  
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5 positive response.  
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### 10 *Statistical analysis*

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12 Best values of spirometric measurements of FEV<sub>1</sub> were used for statistical calculations with  
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14 SPSS<sup>®</sup> Statistics Version 17.0 for Windows<sup>®</sup>. Data were split into two groups: children with  
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16 EIB during the initial visit (defined as a  $\geq 15\%$  fall in FEV<sub>1</sub> after exercise) and children  
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18 without EIB. Further calculations were performed on both groups separately and together.  
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20 The same analysis was performed on children with a  $\geq 10\%$  fall in FEV<sub>1</sub> after the initial  
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22 exercise challenge.  
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27 Baseline percent predicted FEV<sub>1</sub> before both challenges were expressed as mean  $\pm$  SD and  
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29 compared using Student's paired *t* test. Symptom scores on the ACQ and PAQLQ before both  
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31 challenges were compared using Wilcoxon's rank test. Maximum percent fall in FEV<sub>1</sub> after  
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33 both exercise challenges were compared using Student's paired *t* test.  
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37 Spearman's rank order correlation coefficient was calculated for the correlation between ACQ  
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39 and PAQLQ scores and % fall in FEV<sub>1</sub> after exercise.  
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## Results

Research population consisted of 20 children. One child was excluded from analysis because he was not able to perform reproducible spirometry. Data from 19 children were used for analysis (table 1). Among them were 13 boys and 6 girls. Mean age ( $\pm$  SD) was  $11.2 \pm 2.8$  years. Fifteen children were using the combination preparation fluticasone/salmeterol (median dose  $400\mu\text{g}$ ) before the first visit and stepped down to fluticasone monotherapy and 4 children were using the combination preparation budesonide/formoterol (median dose  $400\mu\text{g}$ ) before the first visit and stepped down to budesonide monotherapy. Six children were on a LTRA and six on an intranasal steroid.

Baseline FEV<sub>1</sub> before the initial exercise challenge had a normal distribution with a mean ( $\pm$  SD) of  $94.1 \pm 13.6\%$  predicted value, which was not significantly different from baseline FEV<sub>1</sub> three weeks after the medication reduction ( $94.6 \pm 15.1\%$  predicted value).

Mean maximum heart rate during the first exercise challenge was  $87.6 \pm 4.2\%$  of maximum heart rate, which was not significantly different from mean maximum heart rate during the second challenge ( $87.2 \pm 3.9\%$ ). SABA use was monitored by the asthma control questionnaire (question 6). Before the first exercise challenge (before LABAs were stopped) children reported an average use of 3.4 puffs of SABA per week (including pre-exercise use). After the medication reduction children reported an average use of 4.2 puffs per week.

Mean maximum percent fall in FEV<sub>1</sub> after the first exercise challenge was  $14.5 \pm 10.4\%$ .

Maximum percent fall in FEV<sub>1</sub> after the second exercise challenge was significantly lower ( $p = 0.03$ ), with a mean of  $9.0 \pm 6.5\%$ . (Figure 1 and Figure 2) In 14 children the response to an

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3 exercise challenge, measured by the maximum percent fall in FEV<sub>1</sub>, decreased after the  
4 medication reduction. In 5 children the response to an exercise challenge increased.  
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10 There were 8 children on LABA/ICS combination therapy that experienced EIB; defined by a  
11  $\geq 15\%$  fall in FEV<sub>1</sub> after exercise. This subgroup had a mean maximum percent fall in FEV<sub>1</sub>  
12 after the first exercise challenge of  $25.1 \pm 6.2\%$ . Maximum percent fall in FEV<sub>1</sub> after the  
13 second exercise challenge was significantly lower ( $p < 0.01$ ), with a mean of  $11.6 \pm 8.1\%$ .  
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15 (Figure 3 and Figure 4) In all 8 children, maximum percent fall in FEV<sub>1</sub> after exercise  
16 decreased after the medication reduction. In 6 children, maximum percent fall in FEV<sub>1</sub> was <  
17 15%, indicating they were no longer experiencing EIB.  
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20 There were 11 children on LABA/ICS combination therapy without EIB (fall in FEV<sub>1</sub> <  
21 15%). In this subgroup, there was no change in mean maximum percent fall in FEV<sub>1</sub> after the  
22 medication reduction.(Figure 5) Only one child developed a mild EIB (fall in FEV<sub>1</sub> 17.1%)  
23 after the medication reduction. Analysis using a cutoff of  $\geq 10\%$  fall in FEV<sub>1</sub> provided similar  
24 statistically significant results.  
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41 At the initial visit asthma was generally well controlled with a median [range] score on the  
42 ACQ of 0.86 [3.00]. The children's quality of life was generally not impaired, with a total  
43 median [range] score on the PAQLQ at the initial visit of 5.8 [3.6] and a median score in the  
44 symptoms domain of 6.0 [2.7]. At the second visit median score on the ACQ was 0.71 [3.57],  
45 which was not significantly different from the initial score. Total and symptom scores on the  
46 PAQLQ were respectively 6.3 [3.8] and 6.1 [3.7], which were not significantly different from  
47 the initial scores.  
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3 There was a correlation between scores on the ACQ and PAQLQ (Spearman's rho = 0.43, p =  
4 0.013). There was no correlation between scores on the ACQ or PAQLQ and maximum  
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6 percent fall in FEV<sub>1</sub> after exercise.  
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10 FE<sub>NO</sub> was measured at both visits in 14 patients. Mean ± SD was 16.6 ± 5.9 ppb after  
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12 LABA/ICS combination therapy and 15.6 ± 8.6 ppb after ICS monotherapy. This was not  
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14 significantly different.  
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## Discussion

In this study, we monitored a medication reduction from LABA/ICS combination therapy to monotherapy with the same dose of the ICS in clinically stable asthmatic children. Mean maximum percent fall in FEV<sub>1</sub> after an exercise challenge was significantly lower ( $p = 0.03$ ) after the medication change. In a subgroup of 8 children with a  $\geq 15\%$  fall in FEV<sub>1</sub> after the first exercise challenge, maximum percent fall in FEV<sub>1</sub> reduced in all children after the medication change ( $p < 0.01$ ). Of this subgroup, 6 children had a maximum percent fall in FEV<sub>1</sub>  $< 15\%$  after the second exercise challenge, indicating they were no longer experiencing EIB. This suggests that in asthmatic children on LABA/ICS combination therapy, the cessation of LABA can reduce and in most cases abolish EIB.

To our knowledge, the effect of reducing treatment from LABA/ICS combination therapy to ICS monotherapy on EIB has not yet been studied. According to international guidelines<sup>1,2</sup> treatment choices should be guided by asthma control. Once asthma control is achieved and maintained for at least 3 months, a step down can be considered. When asthma is controlled with LABA/ICS combination therapy, the suggested approach for adults is to reduce the ICS by approximately 25–50 percent every 3 months to the lowest dose possible.<sup>1,2</sup> An alternative that was recently recommended by the FDA<sup>18</sup> is to discontinue the LABA and continue ICS monotherapy at the same dose.<sup>1,2</sup> In adults, reducing the dose of the ICS is considered more effective than switching to an ICS alone.<sup>15-17</sup> The cessation of the LABA could result in a deterioration of asthma control.<sup>15-17</sup> However, the benefits shown in these studies were largely a measure of the beta2-agonist effect, such as improved peak expiratory flow and reduced rescue use of SABAs. On the contrary, a report by Weinberger et al. describes an example of

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3 two adolescent patients whose EIB improved after the replacement of salmeterol with slow-  
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5 release theophylline.<sup>23</sup>  
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10 We analyzed the effect of stepping down treatment on EIB because EIB occurs in the majority  
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12 of asthmatic children and is considered to have a great impact on their quality of life<sup>24</sup>  
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14 (although we found no correlation between the extent of EIB and PAQLQ scores). Measuring  
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16 the airway response to exercise can be used as an indicator of AHR, which is indirectly  
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18 associated with airway inflammation. Titrating treatment guided by AHR leads to fewer  
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20 uncontrolled episodes in adults with asthma<sup>25</sup> and prevented a decline in lung function in  
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22 children with asthma.<sup>26</sup> This suggests that AHR is an indirect marker of asthma control.  
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29 A possible limitation of this study is the lack of a control group in whom we did not change  
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31 the medication regimen. In this pilot study, we decided to analyze regular medication  
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33 reductions, based on clinical decisions. However, the lack of a control group makes this study  
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35 susceptible to bias. The variability in fall in FEV<sub>1</sub> in standardized exercise challenges and  
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37 regression to the mean may have influenced our results. However, children included in this  
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39 study were clinically stable and their asthma was well controlled, as was confirmed by their  
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41 baseline lung function, low FE<sub>NO</sub> levels and ACQ scores. To exclude a learning bias, only  
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43 children who have performed an exercise challenge before were included. The consistent  
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45 decrease in fall in FEV<sub>1</sub> shown in children with EIB (Figure 3) cannot be solely contributed to  
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47 regression to the mean, neither can the mean decrease in maximum percent fall in FEV<sub>1</sub> from  
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49 25.1% to 11.6%. In an epidemiological study by Haby et al reproducibility of the % fall in  
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51 FEV<sub>1</sub> to a standardized exercise challenge was assessed by the calculation of the single  
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53 measurement 95% range. A 95% range of  $\pm 12\%$  was calculated, meaning that there is a 95%  
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3 probability that the true value for a subject is within the range of 12% fall in FEV<sub>1</sub> around the  
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5 single measurement value.<sup>27</sup>  
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8 Exercise challenge responses may be influenced by climatic and environmental factors such  
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10 as circulating allergen. To exclude a seasonal bias, this study was performed outside the main  
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12 pollen season. Second visits were planned 3 weeks after the first visit. There were no  
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14 differences between baseline FEV<sub>1</sub> % predicted, FE<sub>NO</sub> levels and scores on the ACQ and  
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16 PAQLQ before both challenges.  
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19 To optimize adherence, children and their parents were informed about its importance four  
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21 weeks prior to the first exercise challenge and again by a telephonic contact two weeks prior  
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23 to the first exercise challenge. At the first visit to the ice rink, they reported an adherence of  
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25 86 ± 12%.  
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31 A reversal of the previously developed tolerance due to regular use of LABAs could explain  
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33 the reduction in EIB when LABAs were discontinued. Regular use of LABAs leads to  
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35 downregulation of the β<sub>2</sub>AR.<sup>8</sup> This results in a reduction of the duration of the  
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37 bronchoprotective effect of a LABA against EIB<sup>6,7,9,10</sup> and a prolonged recovery time from  
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39 EIB after rescue therapy with a SABA.<sup>11,12</sup> Although corticosteroids increase transcription of  
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41 the β<sub>2</sub>AR-gene, which could theoretically compensate for the downregulation of the β<sub>2</sub>AR<sup>3</sup>,  
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43 tolerance is not prevented by the concomitant use of ICSs.<sup>9,12,28-30</sup>  
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48 In addition to the development of tolerance to the bronchoprotective and bronchodilative  
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50 effects, a growing body of evidence supports the hypothesis that regular use of beta2-agonists  
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52 could increase AHR, especially to allergen.<sup>11,13,31-33</sup> The increase in sputum inflammatory  
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54 cells<sup>31,34</sup> after regular use of beta2-agonists suggests they could paradoxically have a pro-  
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56 inflammatory effect. Regular exposure to LABAs can cause functional desensitization of the  
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3  $\beta$ 2AR in mast cells<sup>35</sup> and airway smooth muscle.<sup>36</sup> The complex signaling pathway  
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5 underlying the relationship between AHR and the  $\beta$ 2AR is still being explored. There appears  
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7 to be a differentiation between downregulation of the  $\beta$ 2AR (causing less effective  
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9 bronchodilatation) and enhanced contractile signaling (causing enhanced AHR) due to  
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11 chronic activation of the  $\beta$ 2AR.<sup>37</sup> Both occur with regular use of beta2-agonists.  
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17 LABAs have been demonstrated to be useful for many patients whose symptoms are not  
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19 adequately controlled with conventional doses of ICS alone<sup>3,4</sup>. However, in this pilot study,  
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21 we demonstrated that in clinically stable asthmatic children on LABA/ICS combination  
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23 therapy, the cessation of the LABA can reduce and in most cases abolish EIB. Therefore, if  
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25 EIB can still be demonstrated in children whose asthma is controlled with LABA/ICS  
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27 combination therapy, changing therapy to ICS monotherapy should be considered. Further  
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29 research is required to determine whether this applies to the general population or to a specific  
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31 subgroup of patients.  
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## Figure Legends

Figure 1. Mean  $\pm$  SD % fall in FEV<sub>1</sub> after exercise challenge after combination therapy and after 3 weeks of treatment with ICS monotherapy.

Figure 2. FEV<sub>1</sub> changes after exercise and after 100  $\mu$ g Salbutamol.

Figure 3. Individual change in % fall in FEV<sub>1</sub> after exercise for those patients with a  $\geq 15\%$  fall in FEV<sub>1</sub> at the first exercise challenge.

Figure 4. Mean  $\pm$  SD % fall in FEV<sub>1</sub> after exercise challenge after combination therapy and after 3 weeks of treatment with ICS monotherapy for those children with a  $\geq 15\%$  fall in FEV<sub>1</sub> at the first exercise challenge.

Figure 5. Individual change in % fall in FEV<sub>1</sub> after exercise for those patients with a  $< 15\%$  fall in FEV<sub>1</sub> at the first exercise challenge.

Table 1. Baseline Characteristics of Research population (N = 19)

	Gender	Age	Medication	Dose ( $\mu\text{g}/\text{day}$ )	LTRA	Baseline FEV <sub>1</sub> % pred.		Postexercise % fall in FEV <sub>1</sub>	
						ICS/LABA	ICS	ICS/LABA	ICS
1	F	10	FP/SAL	500	+	87	84	5.1	9.5
2	M	8	FP/SAL	300	-	93	101	5.4	3.3
3	M	15	BUD/F	400	+	123	125	17.9	16.5
4	M	15	FP/SAL	200	-	90	92	27.0	4.0
5	M	10	FP/SAL	500	-	95	85	17.8	6.3
6	M	11	FP/SAL	200	-	81	86	26.0	6.6
7	F	8	FP/SAL	200	-	94	111	2.2	9.1
8	F	8	FP/SAL	500	-	96	98	9.0	4.4
9	F	8	BUD/F	600	+	78	74	5.7	12.2
10	M	8	FP/SAL	500	+	72	73	25.2	13.3
11	M	8	FP/SAL	500	-	101	105	6.7	3.7
12	F	9	FP/SAL	200	-	99	99	7.9	2.1
13	M	12	BUD/F	400	-	111	113	20.4	8.6
14	M	12	FP/SAL	300	+	99	97	11.2	6.5
15	F	13	FP/SAL	500	-	101	96	5.1	7.1
16	M	14	FP/SAL	500	-	90	85	33.4	29.0
17	M	8	FP/SAL	250	-	94	97	33.3	8.1
18	M	10	FP/SAL	400	+	70	66	3.3	17.1
19	M	16	BUD/F	400	-	115	111	12.4	3.1

FP/SAL = fluticasone propionate / salmeterol

BUD/F = budesonide / formoterol

LTRA = leukotriene receptor antagonist

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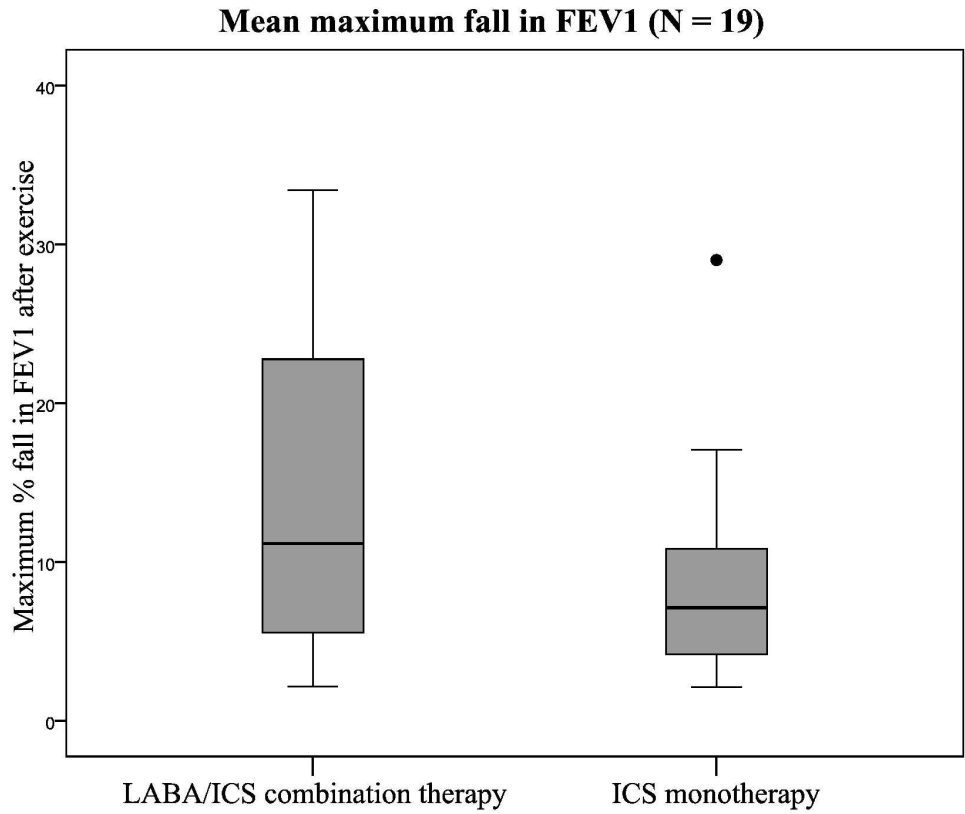


Figure 1. Mean  $\pm$  SD % fall in FEV<sub>1</sub> after exercise challenge after combination therapy and after 3 weeks of treatment with ICS monotherapy.  
144x125mm (600 x 600 DPI)

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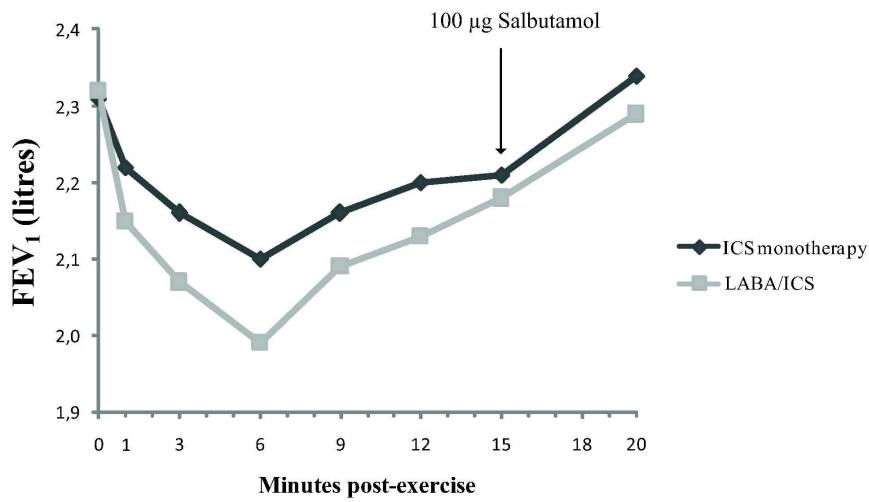


Figure 2. FEV<sub>1</sub> changes after exercise and after 100 µg Salbutamol.  
188x97mm (600 x 600 DPI)

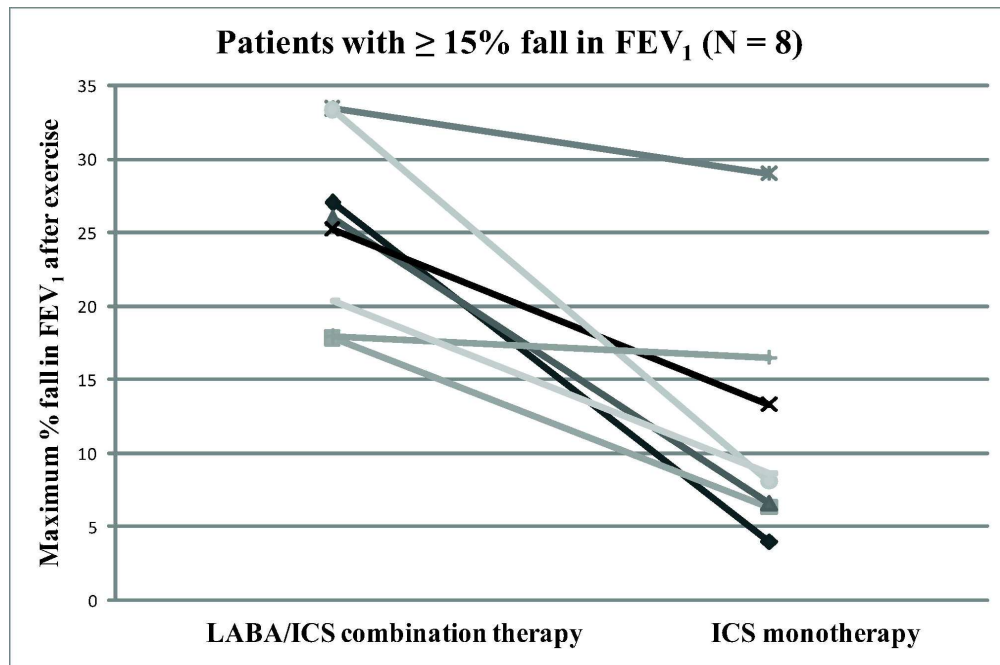


Figure 3. Individual change in % fall in FEV<sub>1</sub> after exercise for those patients with a ≥ 15% fall in FEV<sub>1</sub> at the first exercise challenge.  
 171x112mm (600 x 600 DPI)



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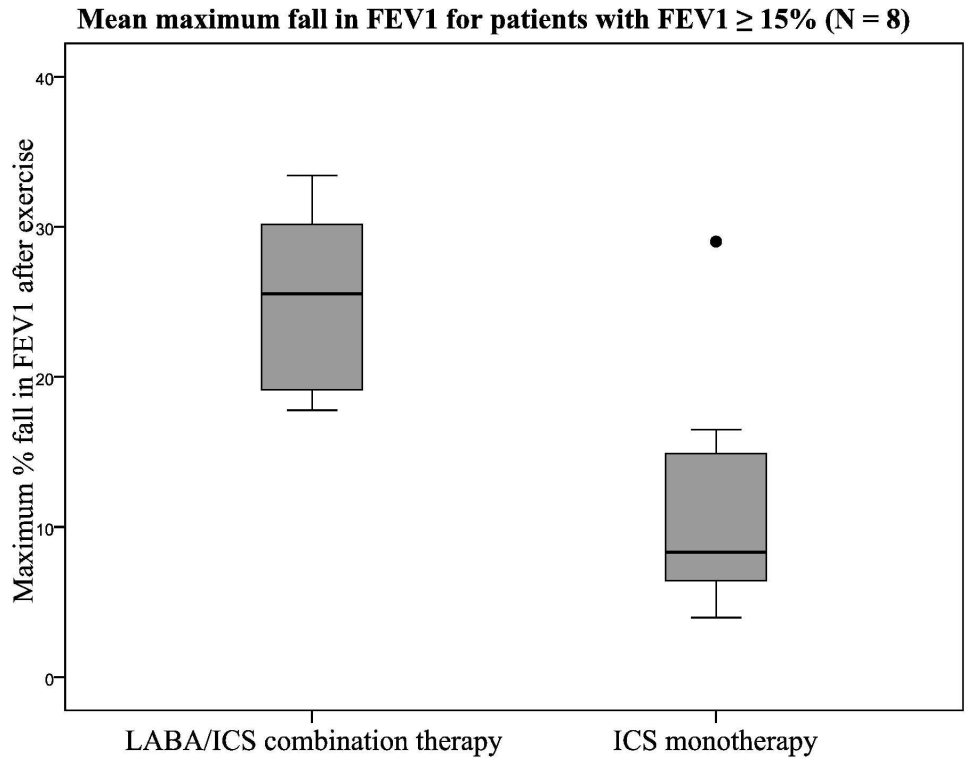


Figure 4. Mean  $\pm$  SD % fall in FEV<sub>1</sub> after exercise challenge after combination therapy and after 3 weeks of treatment with ICS monotherapy for those children with a  $\geq$  15% fall in FEV<sub>1</sub> at the first exercise challenge.  
159x128mm (600 x 600 DPI)

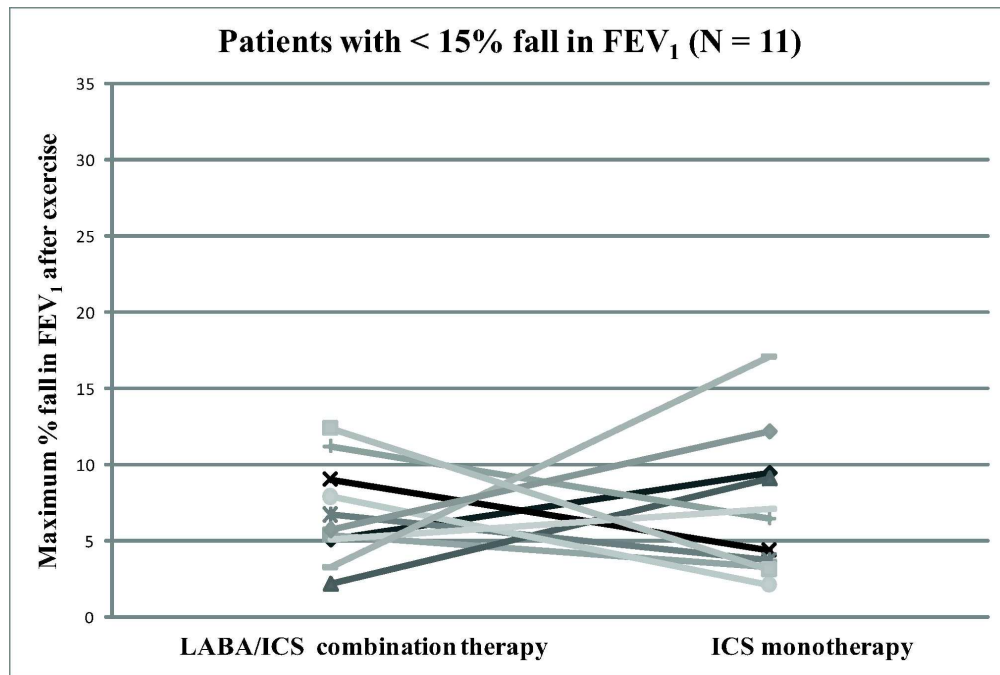


Figure 5. Individual change in % fall in FEV<sub>1</sub> after exercise for those patients with a < 15% fall in FEV<sub>1</sub> at the first exercise challenge.  
171x114mm (600 x 600 DPI)

Review