

Current reviews of allergy and clinical immunology

(Supported by an unrestricted educational grant from Genentech, Inc. and Novartis Pharmaceuticals Corporation)

Series editor: Harold S. Nelson, MD

Is there a problem with inhaled long-acting β -adrenergic agonists?

Harold S. Nelson, MD *Denver, Colo*

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Short-acting β_2 -agonists are effective in relieving acute symptoms of asthma and in the short-term prevention of symptoms from stimuli, such as exercise. They are ineffective when used on a regular schedule to improve asthma control. Long-acting β_2 -agonists, on the other hand, provide sustained bronchodilation and improve asthma control. Regular use of long-acting β_2 -agonists is not associated with significant tolerance to their bronchodilator action, impairment in the response to albuterol, decreased baseline pulmonary function, increased response to methacholine, or increased risk of adverse cardiac events. Case-control studies do not suggest an increased risk for death or intensive care unit admissions with use of long-acting β_2 -agonists. In prospective studies in which there has been an increase in asthma deaths or serious asthma exacerbations, this increased risk has not been observed in subjects using inhaled corticosteroids. Where increased deaths have occurred in relation to either short- or long-acting β_2 -agonists, the events have not occurred equally throughout the exposed population. This suggests that these outcomes were not a direct toxic effect of the drugs and increases the possibility that they resulted from an interaction between relief of symptoms by β_2 -agonists and delay in seeking medical care. (*J Allergy Clin Immunol* 2006;117:3-16.)

Key words: Short-acting β -agonists, long-acting β -agonists, adverse reactions, asthma mortality, β -adrenergic receptor genotypes

Abbreviations used

ACRN: Asthma Clinical Research Network
BAL: Bronchoalveolar lavage
LABA: Long-acting β_2 -adrenergic bronchodilator
OR: Odds ratio
PEF: Peak expiratory flow
RR: Relative risk
SMART: Salmeterol Multicenter Asthma Research Trial

Concerns regarding the use of β_2 -adrenergic agonists in the treatment of asthma originally arose as a result of 2 epidemics of deaths from asthma. The first of these, which lasted from 1959 through 1966, occurred in the United Kingdom and 6 other countries. Deaths in the 5- to 34-year-old age group increased 3-fold. Circumstantial evidence linked this increase in deaths to the introduction of a metered-dose inhaler delivering a higher dose of isoproterenol than that used in other countries.¹ The death rate decreased after widespread publicity about possible overuse of this drug and the importance of closer medical supervision of patients with asthma. In 1976, a sharp increase occurred in asthma deaths in New Zealand. Case-control studies established a link to the use of fenoterol, a β -adrenergic agonist that was somewhat less β_2 selective than albuterol and dispensed at a higher relative dose. A dramatic reduction in the use of fenoterol in New Zealand was temporally associated with a return of mortality caused by asthma to low levels, despite increasing total sales of β -agonists.²

To further explore the relationship between β_2 -adrenergic agonists and asthma deaths, epidemiologists used the health insurance databases from Saskatchewan, Canada. They identified 12,301 patients 5 to 54 years of age for whom at least 10 prescriptions for 1 or more asthma drugs had been dispensed over a 10-year period. From this cohort, they identified 44 who had died from asthma, 85 with a near-death experience and 655 matched control subjects. The initial case-control study found an increased risk of death or near death from asthma was associated with the regular use of inhaled β_2 -agonists. Although the risk with

From National Jewish Medical and Research Center.

Disclosure of potential conflict of interest: H. Nelson has consultant arrangements with Rigel Pharmaceuticals, Protein Design Laboratories, Wyeth Pharmaceuticals, Dynavax Technologies, Altana Pharma US, AstraZeneca, Sanofi-Aventis, Astellas, Genentech/Novartis, Dey Laboratories, Curalogic, GlaxoSmithKline, Inflazyme Pharmaceuticals, Schering-Plough, and Air Pharma; has received grants from Dey Laboratories, Ivax, Rigel, Roche, Wyeth, Astellas, Altana, GlaxoSmithKline, Schering-Plough, Novartis, Medicinova, AstraZeneca, Epigenesis, Eli Lilly, and Sanofi-Aventis; and is on the speakers' bureau for GlaxoSmithKline, Pfizer, AstraZeneca, and Schering-Plough.

Received for publication September 26, 2005; revised October 5, 2005; accepted for publication October 7, 2005.

Reprint requests: Harold S. Nelson, MD, National Jewish Medical and Research Center, 1400 Jackson St, Denver, CO 80206. E-mail: nelsonh@njc.org.

0091-6749/\$32.00

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doi:10.1016/j.jaci.2005.10.013

fenoterol was higher, they also found an increased risk associated with the use of albuterol.³ The group next examined asthma-related and non-asthma-related deaths in the entire cohort. They identified a marked rate of increase in asthma-related deaths beginning with the prescription of 1.4 canisters per month of inhaled β -agonists. They concluded that the strong association between the use of inhaled β -agonists and asthma mortality was confined primarily to the use of these drugs in excess of recommended limits.⁴ The group further analyzed the subset who had used at least 12 inhalers during the 12-month study period. They found that above and beyond the risk previously identified with the number of β -agonist canisters used, a pattern of increasing use of β -agonists over the course of a 6-month period was a major predictive factor for asthma-related death or near-death episodes. The investigators concluded that the greater use of β -agonists was principally a marker of a greater severity of asthma, which itself was associated with an increased risk of fatal or near-fatal asthma and that their data argued against the hypothesis that the β -agonists were causing these adverse effects.⁵

The relationship between fenoterol and the New Zealand epidemic of asthma-related deaths also came under reexamination. An analysis of β -agonist prescribing patterns in Saskatchewan revealed that there was preferred prescribing of fenoterol among users of albuterol who showed signs of increased severity or uncontrolled asthma.⁶ A prospective study in 653 patients from New Zealand found that fenoterol was used more often by patients with severe asthma, and after adjusting for this difference, its use did not increase the risk of severe life-threatening asthma.⁷ Further analysis of the New Zealand epidemic revealed that the increase in asthma-related deaths occurred to the greatest extent in the lowest and somewhat less so in the middle socioeconomic areas, while sparing the economically advantaged areas. Furthermore, the epidemic occurred during a period of dramatic increase in unemployment. This suggested to the authors that financial barriers to health care could have been a contributing factor, along with the availability of a more potent β -agonist inhaler, leading to delay in seeking treatment for asthma exacerbations.⁸

SHORT-ACTING INHALED β -ADRENERGIC BRONCHODILATORS

Prospective clinical studies with short-acting β -agonists

The issue of the possible danger of using β -agonists on a regular basis was raised by a prospective crossover study of regular fenoterol compared with as-needed β_2 -agonists, each for 6 months. Asthma control, on the basis of symptoms, peak flows, and rescue medication use, was better on one of the 2 regimens in 57 of the 64 evaluable subjects, in 30% while receiving regular fenoterol and in 70% while receiving only as-needed β -agonists.⁹ Because fenoterol had been associated with increased asthma-related deaths in New Zealand, it was not clear whether the findings

in this study were unique to fenoterol or applicable to all β -agonists. To further investigate this question, the National Institutes of Health Asthma Clinical Research Network (ACRN) conducted a study in 255 subjects with mild asthma who were not receiving inhaled corticosteroids. For 16 weeks, half of the subjects received 180 μ g of inhaled albuterol 4 times daily plus as-needed albuterol, whereas the other half received only as-needed albuterol. There was no difference in the outcome between the 2 groups in terms of pulmonary function, asthma symptoms, requirement for as-needed albuterol, quality-of-life scores, or response to inhaled methacholine.¹⁰ An even larger and longer trial with a higher dose of albuterol was conducted in England. In a randomized placebo-controlled trial, 983 patients with asthma, 90% of whom were receiving inhaled corticosteroids, were treated with 400 μ g of albuterol 4 times daily or placebo for 1 year. The primary outcome was exacerbations, which were not increased in number, timing, or duration in the albuterol group.¹¹ Although neither of these studies showed any loss of asthma control with regular use of albuterol, they did not show any particular advantage over only as-needed use. The ineffectiveness of the regular use of a short-acting β_2 -agonist for treating asthma was emphasized in the pivotal studies of salmeterol, in which the albuterol 4-times-daily arm offered no advantage over placebo.^{12,13}

Problems with short-acting β -agonists

Unwanted receptor stimulation. Because of the widespread distribution of β_2 -adrenergic receptors, a number of undesired responses result when β_2 -adrenergic agonists are absorbed into the systemic circulation. The principal side effect of β_2 -adrenergic therapy is tremor, which is caused by the direct stimulation of β_2 -adrenergic receptors in skeletal muscle. Increased heart rate and palpitations are less common with the selective β_2 -agonists than with non-selective β_1 - and β_2 -agonists; however, even stimulation of β_2 -adrenergic receptors can result in vasodilatation and reflex tachycardia. Furthermore, some of the β -adrenergic receptors in the atria and ventricles are β_2 in type, and thus direct stimulation of the heart results from the use of even selective β_2 -agonists. β_2 -adrenergic agonists might cause a transient decrease in arterial oxygen tension, often of more than 5 mm Hg. The mechanism of this decrease is probably relaxation of the compensatory vasoconstriction in areas of decreased ventilation combined with increased pulmonary blood flow caused by increased cardiac output. Acute metabolic responses to β_2 -adrenergic agonists include hyperglycemia, hypokalemia, and hypomagnesemia. Because these responses diminish with regular stimulation, such changes are not important in patients receiving long-term therapy.¹⁴

Bronchodilator subsensitivity. A well-recognized effect of the regular administration of β_2 -adrenergic agonists is the development of tolerance (subsensitivity) to the nonbronchodilator effects of the β_2 -agonists, including tremor, tachycardia, prolongation of the QTc interval on the electrocardiogram, hyperglycemia, and hypokalemia.¹⁴ More controversial is whether there is a reduced

bronchodilator response. However, if the first dose of a short-acting β_2 -agonist is preceded by a period of relative β -agonist avoidance, a subsequently diminished bronchodilator response can be readily demonstrated when patients are then treated on a regular basis. The effect is particularly in shortening the duration rather than reducing the peak of bronchodilation.^{15,16} The reduced bronchodilation develops over a period of several weeks and, once established, is stable with continued administration of the same dose of the drug.¹⁷ The clinical significance of this loss of bronchodilator response can be debated. However, if the duration of time that the FEV₁ value remains 15% greater than baseline is used as a measure of continuing significant bronchodilation, this is decreased by approximately 50% as subsensitivity develops.¹⁶ On the other hand, the peak bronchodilator effect is better preserved, and thus the short-acting β_2 -adrenergic bronchodilators continue to perform well as rescue medication, even after development of subsensitivity.

Decrease in FEV₁ and increased response to bronchial challenges. Discontinuation of regular administration of short-acting β_2 -agonists has been followed in some studies by decreases in FEV₁ and increased bronchial responsiveness.¹⁸⁻²¹ These changes are usually observed 8 to 12 hours after cessation of regular treatment with a short-acting β_2 -agonist, and it is not certain how long they persist. Their duration was systematically investigated in a study in which subjects were treated with regular albuterol for 12 weeks and then evaluated 15 hours and 168 hours after stopping treatment. At 15 hours, the FEV₁ had decreased from baseline values of 85.6% to 78.8%, and methacholine sensitivity had increased by 1.17 doubling doses. After 168 hours, the FEV₁ had returned to 85.5%, but the PC₂₀ methacholine, although 0.55 doubling dilutions improved, was still significantly increased.²² The authors suggested that the decrease in FEV₁ represented a transient rebound, whereas the persisting change in methacholine sensitivity might point to a real deterioration of the disease. Pretreatment with 4-times-daily albuterol for 1 week has also been reported to increase the response to exercise challenge.²³ When subjects were tested at least 8 hours after the last dose of albuterol, their baseline FEV₁ was 230 mL lower than after placebo, their FEV₁ decreased 390 mL more after exercise challenge, and they had reduced protection against exercise from pretreatment with albuterol.

Regular treatment with albuterol has also been reported to increase the response to bronchial challenge with inhaled allergen. In a series of studies in which challenges were conducted 8 to 12 hours after the last dose of regular albuterol, there was increased sensitivity to inhaled allergen, as shown by a 0.91 doubling dose decrease in the PC₂₀,²⁴ an increase in the early and late bronchial response to inhaled allergen, and the subsequent increase in methacholine sensitivity.²⁵ Eosinophils and eosinophil cationic protein were increased in induced sputum 7 hours but not 24 hours after the allergen challenge.²⁶ The increased response to allergen after regular albuterol was not prevented by treatment with an inhaled corticosteroid.²⁷

Loss of bronchoprotection. Bronchoprotection is to be distinguished from bronchodilation. Bronchoprotection refers to the ability of pretreatment with a β_2 -agonist to prevent bronchoconstriction caused by a variety of stimuli, including histamine, methacholine, hyperventilation with cold dry air, adenosine, allergens, and exercise. As with subsensitivity to the bronchodilator action of the short-acting β -agonists, partial loss of bronchoprotection is regularly demonstrated if the initial challenge has been preceded by a relative β_2 -agonist-free period.²⁸

Cardiac toxicity. A case-control study was conducted with 1444 individuals who had experienced myocardial infarctions and 4094 matched control subjects.²⁹ In those who had filled a prescription for a β_2 -agonist metered-dose inhaler within 3 months of the index date, there was an increased risk of a myocardial infarction, which was limited to new users of β_2 -agonists who had a history of cardiovascular disease (adjusted odds ratio [OR], 7.32). However, by using the Saskatchewan Health Service databases, a population was formed of all patients given new diagnoses of chronic obstructive pulmonary disease who were older than 55 years of age. All subjects were followed until 1999, death, or their first myocardial infarction. Short-acting β_2 -agonists in any form did not increase the risk of an acute myocardial infarction. First-time use, in particular, also did not increase the risk of myocardial infarction.³⁰ Earlier, this same group had identified 30 cardiovascular deaths among 12,301 patients 5 to 54 years of age. They found that nebulized and oral β_2 -agonists were associated with an OR of 2.4, but β -agonist metered-dose inhalers were not associated with an increased risk of cardiovascular death. The majority of those dying had a significant history of coronary insufficiency or congestive cardiomyopathy.³¹

Some reports suggest the presence of an association between β_2 -agonists and the risk of chronic heart failure.³² It has been suggested that in patients with heart failure, β_2 -agonists augment cardiac function, but with regular exposure to β_2 -agonists, myocardial β_2 -adrenoceptors become desensitized and downregulated.³³ On the other hand, the Asthma β -agonists and Development of Congestive Heart Failure (ABCHF) study failed to confirm an association between asthma, β_2 -agonist use, and the later development of idiopathic dilated cardiomyopathy.³⁴

β_2 -Adrenoceptor genotypes. Identification of genetic polymorphisms in the β -adrenergic receptor has led to investigations into the relation of these genotypes to β_2 -adrenergic function and clinical outcomes. Subjects who participated in 2 earlier studies examining regular treatment compared with as-needed-only treatment^{10,35} were genotyped for the 16th codon of the β_2 -adrenergic receptor, where arginine (Arg) replaces glycine (Gly) in an appreciable percentage of the population. In the ACRN³⁶ study, during the 16 weeks of active treatment, there was a small decrease in the morning peak expiratory flows (PEFs) in patients homozygous for arginine at the 16th codon who used albuterol regularly. This effect increased during a 4-week run-out period during which all patients returned to using only as-needed albuterol. There was no

decrease in PEFs with regular use of albuterol in patients who were homozygous for glycine at the 16th codon. No significant differences in outcomes between regular and as-needed treatment were associated with polymorphisms at the 27th codon of the β_2 -adrenergic receptor. The results of this retrospective analysis were subsequently confirmed in a prospective study by ACRN.³⁷ A 3-way crossover study in 157 patients had compared 6 months of treatment with 400 μ g of albuterol 4 times daily, 50 μ g of salmeterol twice daily, and placebo.³⁵ Retrospective genotyping of the 16th position was performed in 108 of the subjects, of whom 16% were homozygous Arg:Arg, 37% were heterozygous Arg:Gly, and 47% were homozygous Gly:Gly.³⁸ The rate for major exacerbations was significantly greater during treatment with regular albuterol among the homozygous Arg-16 patients compared with placebo, but there was no increase in other genotypes. Morning peak flows were also 7.5 L/min lower in homozygous Arg-16 subjects while receiving regular albuterol, but this did not reach statistical significance.

LONG-ACTING INHALED β_2 -ADRENERGIC BRONCHODILATORS

Prospective clinical studies of the long-acting inhaled β_2 -adrenergic bronchodilators

The inhaled long-acting β_2 -adrenergic bronchodilators (LABAs) salmeterol and formoterol were first shown in single-dose studies to produce sustained improvement in pulmonary function, persisting, on average, for more than 12 hours.^{39,40} Their performance with regular administration was then compared with that of regularly administered short-acting inhaled β_2 -agonists and placebo. These studies demonstrated that the LABAs were superior to both for all outcomes, including improvement in pulmonary function and decrease in both daytime and nighttime symptoms and use of rescue bronchodilators, whereas the results with regular albuterol were for most outcomes no better than those for placebo.^{12,13,41,42} Next, the combination of long-acting inhaled β_2 -agonists with inhaled corticosteroids was examined. Not only were the effects found to be additive, but for all outcomes, the addition of a LABA to an inhaled corticosteroid was superior to administering twice as much of the inhaled corticosteroid.^{43,44} Furthermore, the combination of salmeterol and fluticasone in the same canister was found to offer further advantages over the same doses of the 2 drugs in separate devices. When delivered from one device, there was a significantly greater increase in morning PEF.⁴⁵ Also, the combination of fluticasone with salmeterol in a single inhaler resulted, over a 12-month period, in a 73% increase in the rate of refills over that seen with fluticasone in a separate device.⁴⁶ The comparison of fluticasone alone with the combination of fluticasone and salmeterol was given its ultimate test in the Gaining Optimal Asthma Control (GOAL) study. In this study in 3421 patients with uncontrolled asthma, fluticasone propionate and salmeterol-fluticasone combination were compared in their ability to achieve 2 rigorous

composite, guideline-based measures of control (total control and well controlled).⁴⁷ The inhaled corticosteroid component of treatment was increased at 3-month intervals until total control was achieved or the subject was receiving a maximum of 500 μ g of fluticasone propionate twice a day. Significantly more patients in each of the 3 strata (previously corticosteroid free or previously taking low or moderate doses of corticosteroids) achieved control with the salmeterol-fluticasone combination than with fluticasone alone. Total control after 1 year was achieved by 28% of those receiving fluticasone and 41% receiving the salmeterol-fluticasone combination, whereas well-controlled status after 1 year was achieved by 59% receiving fluticasone propionate and 71% receiving the salmeterol-fluticasone combination.

Problems with LABAs

Bronchodilator subsensitivity. In the Formoterol and Corticosteroids Establishing Therapy (FACET) study there appeared to be a decrease over the first few weeks in morning PEF from the level initially attained on addition of formoterol.⁴⁸ The decrease was small, however, and lung function was maintained at a higher level than with inhaled corticosteroids alone for 1 year, showing no evidence of progressive tolerance. Another study using the LABA formoterol suggested that the initial bronchodilation was not fully retained with chronic administration.⁴⁹ Again, after a small initial decrease, the level of bronchodilation was maintained without further loss. In another study with formoterol, the area under the curve of FEV₁ over 12 hours was unchanged from the initial value after 12 weeks of treatment for the group receiving the 12- μ g dose but was significantly reduced in those receiving 24 μ g twice daily.⁵⁰ A study was specifically designed to examine the development of bronchodilator subsensitivity with formoterol. Subjects received 24 μ g of formoterol or placebo for 4 weeks.⁵¹ After 4 weeks of treatment with formoterol compared with placebo, there was an attenuation of the absolute values of FEV₁ in response to repeated administration of formoterol, which was significant at the last measurement, 6 hours after the last dose of formoterol.

Similar subsensitivity to the bronchodilator action of salmeterol has not been reported.^{12,13,52}

Reduced response to short-acting β -agonists. Several studies have examined the bronchodilator response to albuterol after methacholine-induced bronchoconstriction in subjects who have been given a single week's to several weeks' treatment with the long-acting adrenergic bronchodilators.⁵³⁻⁵⁵ A potential confounder in these studies is the differing prechallenge baseline and differing amounts of methacholine required to produce the same decrease in FEV₁ caused by residual effects of the LABA.

The residual effect on baseline pulmonary function of the LABA also poses a problem with measurement of the response of naturally occurring bronchoconstriction to albuterol. If the differences in baseline are ignored and response is expressed as change from baseline, misleading results can be reported.⁵⁶ This problem is circumvented by expressing the response as the absolute value attained after

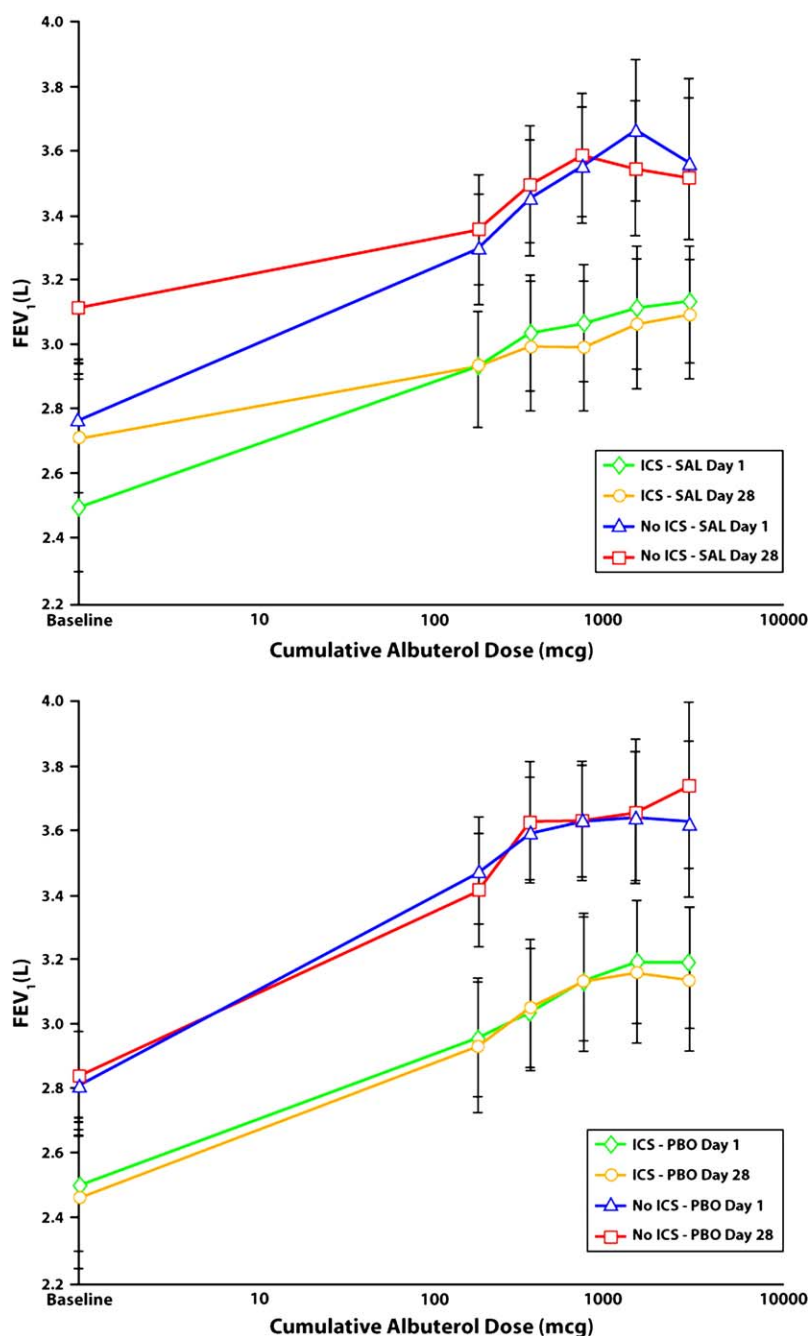


FIG 1. The absolute response to albuterol before and after 28 days of treatment with either 42 μ g of salmeterol (SAL) twice daily (*upper panel*) or placebo (PBO; *lower panel*) in a crossover study with 20 subjects not using (No ICS) and 20 subjects using (ICS) inhaled corticosteroids. Reprinted with permission from Nelson et al.⁵⁷

administration of albuterol. When the response has been expressed in this manner, no reduction in the response to single or multiple doses of albuterol has been observed after regular use of salmeterol.^{57,58} The response to albuterol was preserved both in subjects using and those not using inhaled corticosteroids (Fig 1).⁵⁷

The effect of regular use of salmeterol on the response to albuterol has also been examined in patients presenting to an emergency department with acute asthma.⁵⁹ Fifty-

seven patients had been using salmeterol, and 57 who had not been using salmeterol served as control subjects. In response to nebulized albuterol, mean PEF increased from 45% of predicted value to 62% of predicted value in the control group, a response of 49%, whereas in patients taking salmeterol, there was an increase in PEF of 50% percent from 40% to 60% of predicted value. There also were no significant differences between the 2 groups in the mean length of emergency department stay, the

proportion of subjects admitted to the hospital, or the number of return visits.

The cumulative experience in these 3 studies is reassuring that in the clinical setting there is no reduction in the response to an inhaled short-acting β -agonist taken to relieve symptoms in patients regularly using a LABA or at least salmeterol.

Decrease in FEV₁ and increased response to bronchial challenges. Pulmonary function has been monitored after the discontinuation of both salmeterol and formoterol.^{60,61} With both drugs, the level of pulmonary function gradually decreases to normal, and there is no rebound to less than baseline levels.

Both formoterol and salmeterol provide bronchoprotection against methacholine challenge, which, however, decreases with regular use. This has suggested that there could be a rebound increase in sensitivity to methacholine after discontinuation of long-term treatment. However, methacholine sensitivity has been monitored after discontinuation of salmeterol at 60 hours, 1 week, and 2 weeks, without any evidence of a rebound increase in sensitivity to less than the baseline value.⁶² Similarly, methacholine sensitivity was assessed 12 hours, 36 hours, 60 hours, 108 hours, and 2 weeks after discontinuation of formoterol, with no evidence of methacholine sensitivity increasing beyond the baseline level.⁶¹

The effect of regular treatment with salmeterol on the bronchial response to allergen challenge has been assessed.⁶³ Sixteen patients who had dual asthmatic responses to allergen inhalation were studied after 1 week each of placebo or salmeterol. After posttreatment allergen challenge, there was no difference in bronchoalveolar lavage (BAL) cell counts, but bronchial biopsy specimens revealed significantly increased numbers of submucosal CD45-, CD45Ro-, and AAI-positive cells after salmeterol treatment.

Loss of bronchoprotection. A partial loss of bronchoprotection has been regularly observed with the long-acting adrenergic bronchodilators.^{61,64} The onset of tolerance to bronchoprotection against the bronchoconstriction with methacholine occurs progressively with the second, third, and fourth doses, and this rapid development of tolerance was not affected by use of inhaled corticosteroids.⁶⁵

Protection against exercise-induced bronchoconstriction. As with protection against methacholine, protection against bronchoconstriction after exercise by salmeterol and formoterol decreases with their regular use.^{66,67} Even with once-daily administration of salmeterol and regular use of inhaled corticosteroids, there was significant loss in the degree of protection 1 and 9 hours after exercise after 1 month.⁶⁸ In an 8-week study in adults, protection at the beginning was similar with montelukast and salmeterol, but after 8 weeks, the percentage inhibition in the decrease in FEV₁ was 57% with montelukast and 33% with salmeterol.⁶⁹

Cardiac toxicity. In patients with mild-to-moderate asthma, there was no difference between the maximum effects of 12 μ g of formoterol and placebo on heart rate, blood pressure, QTc interval, and plasma potassium level.

The 24- μ g dose significantly decreased plasma potassium levels. The 2 highest doses, 48 and 96 μ g, affected most of the variables.⁷⁰ A review of 17 studies involving 1443 patients who received 50 μ g of salmeterol twice daily found no increase in cardiovascular adverse effects with salmeterol compared with placebo. Holter data revealed no episodes of sustained ventricular tachycardia and no clinically significant differences in 24-hour heart rate, ventricular and supraventricular ectopic events, qualitative electrocardiograms, QT intervals, or vital signs between the salmeterol treatment group and the placebo group.⁷¹ Similar findings were seen when patients were stratified according to age and the known presence of cardiovascular disease. The risk of nonfatal cardiac failure and ischemic heart disease was investigated in 3 cohorts of British patients receiving at least one prescription for nedocromil, salmeterol or bambuterol. The risk of cardiac failure was increased 3.4-fold among patients prescribed bambuterol compared with nedocromil. The risk was greatest during the first month of treatment. There was also a 4-fold increased risk of ischemic heart disease during the first month of bambuterol treatment, which rapidly decreased to the same rate as seen in patients prescribed nedocromil. There was no increase in the risk of either outcome among patients prescribed salmeterol.⁷²

β_2 -Adrenoceptor genotype. A retrospective analysis of the influence of β_2 -adrenoceptor polymorphism on the response to salmeterol was conducted in a 3-way crossover study in 157 patients that had compared 6 months of treatment with 400 μ g of albuterol 4 times daily, 50 μ g of salmeterol twice daily, and placebo.³⁵ Retrospective genotyping of the 16th position was performed in 108 of the subjects, of whom 16% were homozygous Arg:Arg.³⁸ As opposed to the results in the albuterol arm, in which the morning PEFs were lower and the rate for major exacerbations was significantly greater among the homozygous Arg-16 patients compared with those receiving placebo, in the salmeterol arm Arg:Arg-16 subjects had a higher morning PEF and reduction in the occurrence of major exacerbations compared with those in the placebo arm (Fig 2).³⁸ Additional reports on the effect of β_2 -adrenoceptor polymorphisms have appeared in abstract form.^{73,74} These studies found no difference in the 12-week response to salmeterol (in combination with fluticasone) assessed on the basis of changes in morning PEF, symptoms, or albuterol use between 57 patients with Arg:Arg-16 and 187 patients with Arg:Gly or Gly:Gly genotypes of the β -adrenergic receptor. The rate of exacerbations was not increased in 29 Arg:Arg-16 patients compared with 154 with Arg:Gly or Gly:Gly-16 genotypes after 12 weeks of treatment with the fluticasone-salmeterol combination.⁷⁴

The effect of long-acting adrenergic agonists on airway inflammation

The effect of the LABAs on airway inflammation has been examined during monotherapy compared with placebo or during add-on therapy to inhaled corticosteroids in comparison with unchanged or higher doses of inhaled

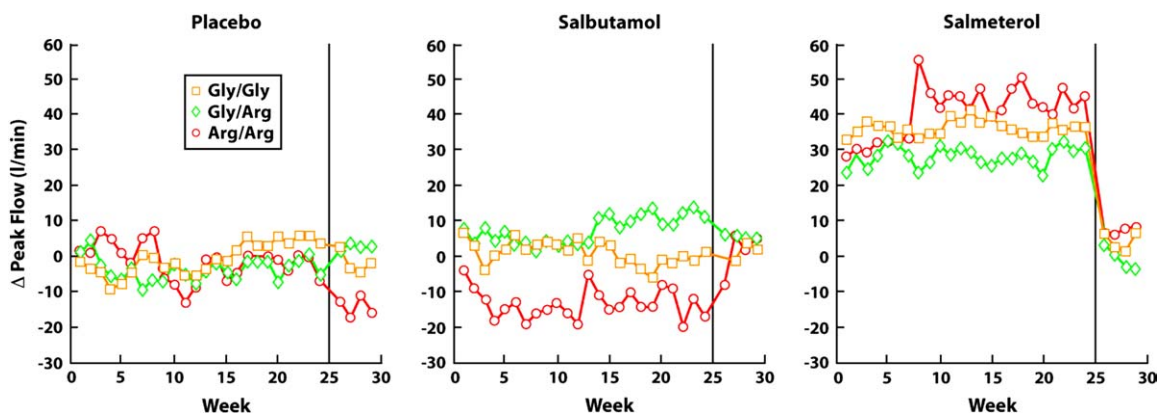


FIG 2. The effect of β -adrenergic receptor genotypes on morning PEF during 6 months of treatment with placebo, albuterol 4 times daily, or salmeterol twice daily. Whereas the trend is for morning PEF to be lower in the Arg:Arg-16 subjects while receiving regular albuterol, 400 μ g twice daily, these same subjects tended to have higher morning PEFs while receiving salmeterol, 50 μ g twice daily. Similar differences were observed in the rate of asthma exacerbations. Reprinted from Taylor et al³⁸ with permission from the BMJ Publishing Group.

corticosteroids. When the inflammatory response during monotherapy with salmeterol has been compared with that during placebo treatment, there have generally been no differences in airway inflammation as assessed by using BAL, induced sputum, or bronchial biopsy.^{75,76} Exceptions have been the demonstration of reduced blood vessels in the lamina propria after 3 months of treatment with salmeterol⁷⁷; reduction in bronchial wall mast cells and eosinophils with 24 μ g of formoterol twice daily for 9 weeks,⁷⁸ and reduction after 6 weeks of treatment with salmeterol of neutrophils in bronchial biopsy specimens and concentrations of myeloperoxidase and soluble E-selectin in serum.⁷⁹ When a LABA is added to a low dose of inhaled corticosteroids and compared with a higher dose, the control of airway inflammation is usually as good⁸⁰ or better with the lower dose of inhaled corticosteroid plus the LABA. Fifty patients symptomatic on 100 to 500 μ g/d inhaled corticosteroids were randomly placed on added treatment with placebo, 50 μ g of salmeterol, or 100 μ g of fluticasone twice daily for 12 weeks. Those receiving salmeterol had a significant decrease in EG1-positive eosinophils in the lamina propria (18.3 $\rightarrow$ 7.6 cells/mm), whereas those receiving fluticasone had a decrease in BAL lymphocyte activation but no significant change in eosinophils.⁸¹ Fifty-six asthmatic subjects whose symptoms were previously not well controlled with inhaled corticosteroids were randomized to 3 months of treatment with 200 μ g of fluticasone alone or with added salmeterol or to 500 μ g of fluticasone, all given twice daily.⁸² The only significant change was a significant decrease in mast cells in the bronchial biopsy specimens in those receiving low-dose fluticasone plus salmeterol.

Monotherapy with LABAs

Because the LABAs lack consistent anti-inflammatory effects, they are not recommended for use as monotherapy by the National Heart, Lung, and Blood Institute “Guidelines for the diagnosis and treatment of asthma.”⁸³

Perhaps the best evidence to support this positioning is the study known as Salmeterol or Corticosteroid (SOCS). In this study in adolescents and adults, the National Institutes of Health Asthma Clinical Research Network examined the effect of randomizing patients whose symptoms were well controlled with the inhaled corticosteroid to either continue on the inhaled corticosteroid or be switched to salmeterol or placebo.⁸⁴ Although pulmonary function and symptoms continued to be controlled in the patients who were started on salmeterol, there was evidence of increasing airway inflammation evidenced by sputum eosinophilia and increases in exhaled nitric oxide and the response to inhaled methacholine. Both treatment failures and asthma exacerbations were greater in those on salmeterol monotherapy than in those who remained on inhaled corticosteroids. The lack of effectiveness of monotherapy with salmeterol was confirmed in two 1-year studies in children that compared monotherapy with salmeterol with monotherapy with beclomethasone. In one study in 67 children, FEV₁ and methacholine sensitivity both improved more with beclomethasone dipropionate, whereas exacerbations of asthma were more frequent with salmeterol (17 vs 2).⁸⁵ In the other study, a placebo-controlled study in 241 children, similar results were obtained. Beclomethasone was superior for reduction in asthma symptoms, albuterol use, and improved airway hyperresponsiveness and was associated with fewer withdrawals because of asthma exacerbations.⁸⁶

Masking inflammation

A recurrent concern is that LABAs, by providing symptomatic improvement, might mask the presence of bronchial inflammation and thereby leave the asthmatic patient at risk for more severe exacerbations. This concern was addressed in a crossover study in which high-dose inhaled corticosteroids (≥ 1500 μ g/d beclomethasone equivalent) were tapered while subjects received either placebo or salmeterol.⁸⁷ Salmeterol treatment allowed a

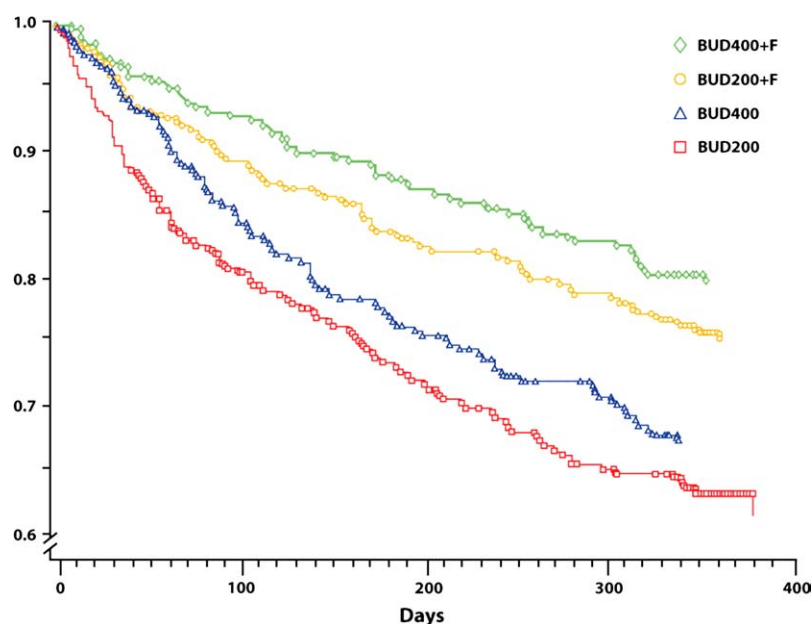


FIG 3. The effect on the rate of asthma exacerbations of 2 doses of budesonide (*BUD*) with or without the addition of formoterol (*F*) in patients previously treated with low doses of inhaled corticosteroids. Reprinted with permission from O'Byrne et al.⁴⁴

greater reduction in steroid dose before an exacerbation developed. The week before the exacerbation, eosinophils in induced sputum had increased to 19.9% in the salmeterol arm versus 9.3% in the placebo arm. This finding was interpreted as evidence for masking of inflammation by salmeterol. However, because 9 of 13 subjects were tapered completely off inhaled corticosteroids while receiving salmeterol, it really confirms what others have shown, that monotherapy with LABAs is not appropriate.

Exacerbations

Because deaths from asthma are fortunately rare, many studies have examined near-fatal attacks as a surrogate outcome. It has been shown that asthmatic patients who have respiratory failure or impaired consciousness or require intubation, admission to an intensive care unit, or both are similar in many ways to patients who died, including in terms of their regular use of medication.⁸⁸ The first study that suggested that the addition of a LABA to an inhaled corticosteroid could reduce the occurrence of major exacerbations of asthma was the Formoterol and Corticosteroids Establishing Therapy study.⁴⁸ Although the single most successful strategy for reducing major exacerbations of asthma (those requiring prednisone or with a decrease in PEF of $\geq 30\%$ for 2 consecutive days) was a quadrupling of the dose of budesonide (from 200 $\mu\text{g}/\text{d}$ to 800 $\mu\text{g}/\text{d}$), the addition of formoterol to either low- or high-dose budesonide further reduced both minor and major exacerbations. This effect of the addition of a LABA to an inhaled corticosteroid in reducing asthma exacerbations was confirmed in the Optimal Treatment for Mild Asthma (OPTIMA) study,⁴⁴ in which the addition of formoterol to 200 μg of budesonide was more effective at preventing exacerbations than 400 μg alone (Fig 3),⁴⁴ and by an

analysis of 9 studies in which the addition of salmeterol to low-dose inhaled corticosteroid was compared with at least doubling the dose of inhaled corticosteroids.⁴³ Once again, the addition of the LABA was more effective in preventing exacerbations of asthma. Even more striking was the analysis of the exacerbations that occurred in subjects treated with 88 μg of fluticasone plus salmeterol or 220 μg of fluticasone, each twice daily.⁸⁹ Not only was the rate of exacerbations reduced from 13.8% to 8.8%, but the mean duration of exacerbations was reduced from 10.5 to 8.4 days. Further analysis of these exacerbations revealed that the difference was due to a more rapid improvement after the institution of prednisone in those receiving the combination therapy (Fig 4).⁸⁹

The greater reduction in exacerbations with combination therapy with inhaled corticosteroids and long-acting β -agonists than with higher doses of inhaled steroids alone received scientific support from *in vitro* studies showing that the combination of fluticasone and salmeterol is able to control peripheral blood T-cell activation more effectively than fluticasone alone and with a lower concentration of steroid.⁹⁰ Corticosteroids have long been known to upregulate the β -adrenergic receptor.⁹¹ There are now *in vitro* data indicating that the long-acting β -agonist primes the glucocorticoid receptor, facilitating activation by corticosteroids.⁹²

Spontaneous reports and retrospective studies

The introduction of salmeterol was followed by several reports of adverse events, including a report of 6 patients who experienced breathlessness, wheeze, or cough after salmeterol.⁹³ These patients experienced the same

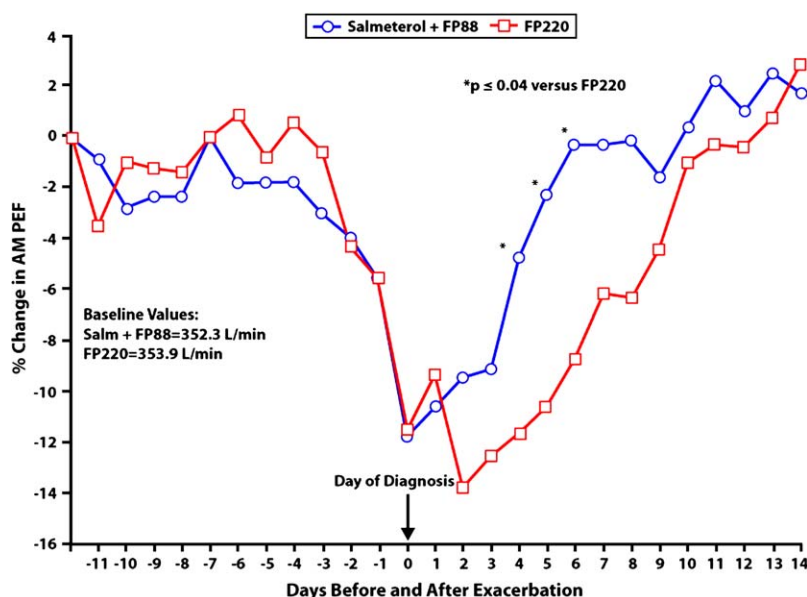


FIG 4. Onset and recovery from asthma exacerbations in patients receiving 88 µg of fluticasone twice daily plus salmeterol twice daily or receiving 220 µg of fluticasone twice daily. At the time the exacerbation was diagnosed, the subjects were started on prednisone. The improvement was faster in subjects receiving low-dose fluticasone plus salmeterol than in those receiving the higher dose of fluticasone alone. The differences were statistically significant at several time points, as indicated by asterisks. Reprinted with permission from Matz et al.⁸⁹

immediate decrease in FEV₁ after placebo, suggesting the problem was the slow onset of bronchodilation with salmeterol. More serious were reports of respiratory arrests in 3 young asthmatic subjects occurring 1 to 4 weeks after starting salmeterol⁹⁴ and of 2 elderly patients who had fatal respiratory arrests at home and were found holding their salmeterol inhalers.⁹⁵

As opposed to these anecdotal reports, several retrospective analyses have been conducted to determine whether there was a relation between salmeterol use and poor asthma outcomes. A postmarketing survey was conducted in the United Kingdom in which information was obtained from physicians on 15,407 patients who were given salmeterol and observed for a minimum of 1 year.⁹⁶ There were 73 asthma deaths, but only 39 of these were in patients still taking salmeterol in the last month of life. Review of patient records identified only 4 deaths in which a temporal relationship between death and the use of salmeterol made it difficult to exclude a possible association. The study suggested that advanced age and severity of disease were the most likely factors contributing to asthma mortality in the population studied. A case-control study was conducted of 48 patients with asthma admitted to the intensive care unit for asthma in Wessex in 1992.⁹⁷ The adjusted relative risk (RR) of a near-fatal attack of asthma in patients prescribed salmeterol was 1.42 for chronically severe patients. This suggested to the authors that the use of salmeterol by patients with chronic severe asthma was not associated with a significantly increased risk of a near-fatal attack of asthma. By using automated health insurance claims, 2709 recipients of salmeterol were identified and compared with 3825 recipients of slow-

release theophylline.⁹⁸ After adjusting for baseline factors, including severity, incidence rates of severe asthma in the salmeterol recipients were not increased for emergency care (RR, 0.69), hospitalization (RR, 1.09), or intensive care unit stays (RR, 0.81). A nested case-control analysis was performed on the UK General Practice Research database.⁹⁹ First-time users of salmeterol (8386), ipratropium (4305), or theophylline (4228) between January 11, 1992, and April 30, 1995, were followed for 16 weeks. After adjusting for risk factors, the RR estimates of a respiratory death compared with those seen in salmeterol users were 1.8 for ipratropium and 3.0 for theophylline. It was concluded that salmeterol use was not associated with an increase in short-term mortality compared with ipratropium and theophylline. Data covering 27% of the population of Great Britain for the years 1994 through 1998 were examined in a case-control study.¹⁰⁰ Five hundred thirty-two patients younger than 65 years who died from asthma and a like number of matched control subjects with a hospital admission for asthma were compared. There was no significant association with drugs prescribed in the 4 to 12 months before the index date. LABAs, mostly salmeterol, were prescribed for 38% of the control subjects. After adjusting for severity, the OR associated with LABA prescription in the 1 to 5 years before the index date was 0.74, suggesting, if anything, a decreased association with mortality.

Prospective studies of mortality associated with the LABAs

Shortly after approval of salmeterol in the United Kingdom, a 16-week, randomized, double-blind clinical

TABLE I. Serious asthma exacerbations in subjects receiving formoterol¹⁰³

Serious asthma exacerbations	Formoterol, 12 μ g twice daily (n = 527)	Formoterol, 24 μ g twice daily (n = 527)	Formoterol, 12 μ g twice daily plus as needed (n = 517)	Placebo (n = 514)
All subjects	5	2	1	1
Subjects receiving inhaled corticosteroids	3	0	0	1
Exacerbations treated with prednisone	31 (5.9%)	33 (6.3%)	23 (4.4%)	45 (8.8%)

trial was undertaken in which 50 μ g of salmeterol twice daily was given to 14,113 and 200 μ g of albuterol 4 times daily was given to 7082 patients with asthma. Sixty-nine percent in each treatment group were using inhaled corticosteroids.¹⁰¹ Twelve deaths occurred in the salmeterol group compared with 2 in the albuterol group, for an RR of 3.0 and a *P* value of .105. However, asthma overall did not appear to worsen in those receiving salmeterol because the RR with salmeterol for asthma hospitalization was 0.95, and that for withdrawals because of asthma was 0.77.

Concerns have been expressed regarding the safety of formoterol when administered at the unapproved dose of 24 μ g twice daily.¹⁰² The authors analyzed 3 prospective, randomized, placebo-controlled, double-blind clinical trials of formoterol, 12 μ g twice daily and 24 μ g twice daily. They observed that more patients treated with 24 μ g of formoterol twice daily experienced serious asthma exacerbations than did patients who had been treated with placebo. In the two 12-week studies in adolescents and adults, 9 (3.3%) of 271 who received 24 μ g twice daily experienced exacerbations that required hospitalization and resulted in 1 death and 2 intubations. This was in comparison with 2 patients receiving placebo, 2 patients receiving 4-times-daily albuterol, and 1 patient receiving 12 μ g twice daily who had serious exacerbations. In a yearlong pediatric study there were 11 serious exacerbations in the group receiving 24 μ g twice daily (6.4%) and 8 in those receiving 12 μ g twice daily (4.7%), whereas there were none in the placebo group. There was, however, no difference among the groups in total number of exacerbations or withdrawals because of asthma.

As a consequence of these findings, a prospective phase IV study was conducted with formoterol.¹⁰³ This 16-week, randomized, double-blind, placebo-controlled study compared the occurrence of asthma exacerbations in 2085 subjects 12 years of age or older with a mean FEV₁ of 69% of predicted value who were started on 12 μ g of formoterol twice daily, 24 μ g of formoterol twice daily, or 12 μ g of formoterol twice daily plus up to 2 additional as-needed doses or placebo.

The conclusion was that the incidence of serious adverse events was low and similar across treatment groups (Table I).¹⁰³

The Salmeterol Multicenter Asthma Research Trial (SMART)

In 1996, a multicenter, randomized placebo-controlled study was begun to compare the safety of salmeterol added to usual asthma therapy compared with the usual asthma therapy alone.¹⁰⁴ Subjects were seen once in the investigator's clinic, at which time they were issued a 7-month supply of study medication. Subsequent contact with the subject was by telephone from a central office scheduled every 4 weeks. The target was 60,000 participants. A planned interim analysis was conducted after approximately half the subjects were enrolled. At that time, although predefined criteria for stopping the study were not met, it was elected to terminate the study because of preliminary findings in African American subjects and difficulty in enrolling subjects. A major cause for this difficulty in recruitment was the exclusion of any subject who had previously used a long-acting β -agonist.

As a result of the findings from the interim analysis, the US Food and Drug Administration imposed a "black box" warning on both salmeterol and the salmeterol-fluticasone combination. The wording of this warning has been as follows (Serevent Diskus package insert; GlaxoSmithKline, Research Triangle, NC):

Data from a large placebo-controlled US study that compared the safety of salmeterol (SEVREVENT® inhalation Aerosol) or placebo added to usual asthma therapy showed a small but significant increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patents treated for 28 weeks) versus those on placebo (3 of 13,179). (see WARNINGS and CLINICAL TRIALS).

In the "Warnings" section of the package insert is the following:

DATA FROM A LARGE PLACEBO-CONTROLLED SAFETY STUDY THAT WAS STOPPED EARLY SUGGEST THAT SALMETROL MAY BE ASSOCIATED WITH RARE SERIOUS ASTHMA EPISODES OR ASTHMA-RELATED DEATHS. Data from this study further suggest that the risk might be greater in African American patients. The data from the Salmeterol Multicenter Asthma Research Trial (SMART) study are not adequate to determine whether concurrent use of inhaled corticosteroids provides protection from this risk.

How should a physician respond to this information? The warning appropriately alerts the physician to findings of which he or she should be aware. Clearly the best course for the physician is to become familiar with the results of the SMART study to be able to make an informed judgment as to whether this information is relevant to the patient for whom he or she is considering prescribing

TABLE II. Combined asthma-related death or life-threatening experiences in the SMART study by use of inhaled corticosteroids at baseline¹⁰⁴

Category	Salmeterol (n = 13,176)	Placebo (n = 13,179)
Baseline ICS use	16	13
African American ICS use	9	3
No baseline ICS	21	9
African American no ICS use	10	1

ICS, Inhaled corticosteroid.

salmeterol or the salmeterol-fluticasone combination. The details of the outcomes of the SMART study follow.

The study population of 26,355 was 72% Caucasian and 18% African American. There was an imbalance in markers of asthma severity between those 2 populations. The African American subjects' baseline PEFs were 7.2% of predicted value lower, and emergency department visits and hospitalizations in the previous 12 months were 41% and 15%, respectively, compared with 22% and 6% for the Caucasian subjects. Furthermore, only 38% were using inhaled corticosteroids at baseline compared with 49% of the Caucasian subjects.

The occurrence of the primary outcome, respiratory-related deaths or life-threatening experiences (intubation and mechanical ventilation), was not significantly different for salmeterol versus placebo (50 vs 36 subjects). There was a small but significant increase in respiratory-related (24 vs 11 subjects) and asthma-related (13 vs 3 subjects) deaths and in combined asthma-related deaths or life-threatening experiences (37 vs 22 subjects) in subjects receiving salmeterol versus placebo. The imbalances occurred largely in the African American subpopulation (respiratory-related deaths or life-threatening experiences [20 vs 5] and asthma-related deaths or life-threatening experiences [19 vs 4] in subjects receiving salmeterol vs placebo). Deaths occurred in 7 patients who were receiving inhaled corticosteroids at baseline, 4 of whom were randomized to salmeterol and 3 to placebo, whereas in those patients not receiving inhaled corticosteroids at baseline, all 9 deaths occurred in patients randomized to salmeterol (Table II).¹⁰⁴

Two methods of recruitment were used during the study. Initially, subjects were recruited through print, radio, and television advertising and were assigned to a study investigator by geographic location (1996-1999). When recruitment waned, the method of recruitment was changed. The large-scale advertising campaign was stopped, and during 2000 through 2003, additional study investigators were added to facilitate enrollment. During phase II, subjects were recruited directly by the study investigators. There was a marked difference in the occurrence of asthma-related death and life-threatening experiences between the 2 phases (Table III).¹⁰⁴ Although only 58.2% of the subjects were enrolled in phase I, they experienced 81.4% of the adverse outcomes. Thus subjects were more than 3 times as likely to die or

TABLE III. Combined asthma-related death or life-threatening experience by recruitment phase¹⁰⁴

Outcome	Phase I		Phase II	
	Sm (n = 7670)	PI (n = 7672)	Sm (n = 5506)	PI (n = 5506)
Deaths and LTE	31 (0.4%)	17 (0.22%)	6 (0.1%)	5 (0.09%)
Deaths	10	3	3	0
African American subjects	7%	17%	19%	19%

Sm, Salmeterol; PI, placebo; LTE, life-threatening experience.

have a life-threatening experience if they were recruited in the first phase. This was not accounted for by an ethnic imbalance because African Americans constituted 17% of subjects in phase I and 19% of subjects in phase II.

In conclusion, the association of salmeterol in the SMART study with an overall significant increase in asthma-related deaths or deaths and life-threatening experiences compared with placebo is unarguable. However, the nearly equal occurrence of asthma-related deaths and life-threatening experiences in the salmeterol and placebo cohorts in those using inhaled corticosteroids at baseline (16 vs 13) and in those recruited by the investigators in phase II (6 vs 5) suggests caution in assuming that the nature of this association is known.

CONCLUSIONS

Short-acting β -adrenergic bronchodilators

1. Short-acting β -adrenergic bronchodilators are effective in relieving acute symptoms of asthma and, in the short term, prevention of symptoms from stimuli, such as exercise.
2. On the other hand, short-acting β -agonists are ineffective when used on a regular schedule to improve asthma control.
3. With frequent administration, short-acting β -agonists incur some loss of bronchodilation and decrease in bronchoprotective action.
4. Regular albuterol treatment of patients with the Arg: Arg-16 genotype of the β_2 -adrenergic receptor results in a decrease in morning PEF and an increase in asthma exacerbations.
5. There is, at most, on stopping regular administration a very transient rebound decrease in pulmonary function and increase in bronchial hyperresponsiveness.
6. Cardiac toxicity is largely associated with nebulized and oral preparations.
7. Use, and especially frequent use, of short-acting β_2 -agonists has been associated with increased risk of death and near-death from asthma. However, studies suggest that the increased use of short-acting β_2 agonists in these situations is symptomatic of poor asthma control, which is the underlying cause of the untoward outcomes.

LABAs

1. LABAs provide sustained bronchodilation and improve asthma control.
2. LABAs by themselves have no significant anti-inflammatory effects and hence should be used in conjunction with inhaled corticosteroids.
3. LABAs added to inhaled corticosteroids enhance asthma control and decrease the occurrence of asthma exacerbations more effectively than does a doubling of the dose of inhaled corticosteroid.
4. In combination with inhaled corticosteroids, there is some evidence to suggest an enhanced effect on airway inflammation by the addition of long-acting β -agonists.

Potential problems with LABAs

1. A minor degree of tolerance to the bronchodilator activity of formoterol has been demonstrated but not to salmeterol.
2. Regular use of salmeterol is not associated with any decrease in the absolute level of lung function attained with administration of albuterol, either in patients with stable asthma or in patients presenting with acute asthma symptoms.
3. There is no evidence for either a rebound increase in methacholine sensitivity or a decrease in baseline pulmonary function during interruptions in LABA therapy.
4. There is a partial loss of protection against exercise-induced bronchoconstriction with regular use of either of the long-acting β -agonists.
5. Significant cardiac risk has not been documented with approved doses of the long-acting β -agonists.
6. There is currently no evidence that the response to LABAs is affected by β -adrenoceptor genotype. This question is the subject of ongoing studies.

LABA effects on asthma control and mortality

1. Large retrospective case-control studies of asthma exacerbations and deaths have failed to implicate LABAs as a risk factor for hospitalization, intensive care unit admissions, or death.
2. Prospective studies of both salmeterol and formoterol have identified an increased risk for death or near-fatal outcome, while not suggesting an overall worsening of asthma control in the treated population.
3. Studies have not identified an increased risk of deaths or near-fatal outcomes in patients using both LABAs and inhaled corticosteroids.
4. Reanalysis of the pattern of asthma deaths from New Zealand in relation to the socioeconomic status of areas of residence of those with fatal asthma attacks and the relation of deaths in the SMART study to method of recruitment suggest that the isolated deaths are not due to a direct toxic effect of the β -agonists. Rather, the data support an alternative hypothesis that in patients with limited access to medical care, the symptomatic relief provided by β -agonists might result in delay in seeking medical care in the face of increasing airway inflammation.

In conclusion, LABAs should only be administered to patients with asthma accompanied by therapy with inhaled corticosteroids. In this combination there is no evidence of deleterious effects from use of the LABAs, and the combination results in better control of asthma and a reduction in asthma exacerbations compared with up to twice as high a dose of inhaled corticosteroids used alone.

REFERENCES

1. Stolley PD, Schinnar R. Association between asthma mortality and isoproterenol aerosols: a review. *Prev Med* 1978;7:519-38.
2. Pearce N, Beasley R, Crane J, Burgess C, Jackson R. End of the New Zealand asthma mortality epidemic. *Lancet* 1995;345:41-4.
3. Spitzer WO, Suissa S, Ernst P, Horwitz RI, Habbick B, Cockcroft D, et al. The use of β -agonists and the risk of death and near death from asthma. *N Engl J Med* 1992;326:501-6.
4. Suissa S, Ernst P, Boivin J-F, Horwitz RI, Habbick B, Cockcroft D, et al. A cohort analysis of excess mortality in asthma and the use of inhaled β -agonists. *Am J Respir Crit Care Med* 1994;149:604-10.
5. Suissa S, Blais L, Ernst P. Patterns of increasing beta-agonist use and the risk of fatal or near-fatal asthma. *Eur Respir J* 1994;7:1602-9.
6. Blais L, Ernst P, Suissa S. Confounding by indication and channeling over time: the risks of beta2-agonists. *Am J Epidemiol* 1996;144:1161-9.
7. Garrett JE, Lanes SF, Kolbe J, Rea HH. Risk of severe life threatening asthma and beta agonist type: an example of confounding by severity. *Thorax* 1996;51:1093-9.
8. Garrett J, Kolbe J, Richards G, Whitlock T, Rea H. Major reduction in asthma morbidity and continued reduction in asthma mortality in New Zealand; what lessons have been learned? *Thorax* 1995;50:303-11.
9. Sears MR, Taylor DR, Print CG, Lake DC, Li QO, Flannery EM, et al. regular inhaled B-agonist treatment in bronchial asthma. *Lancet* 1990; 336:1391-6.
10. Drazen JM, Israel E, Boushey HA, Chinchilli VA, Fahy JE, Lazarus SC, et al. Comparison of regularly scheduled with as-needed use of albuterol in mild asthma. *N Engl J Med* 1996;335:841-7.
11. Dennis SM, Sharp SJ, Vickers MR, Frost CD, Crompton GK, Barnes PJ, et al. Regular inhaled salbutamol and asthma control: the TRUST randomized trial. *Lancet* 2000;355:1675-9.
12. Pearlman D, Chervinsky P, LaForce C, Seltzer JM, Southern DL, Kemp JP, et al. A comparison of salmeterol with albuterol in the treatment of mild-to-moderate asthma. *N Engl J Med* 1992;327:1420-5.
13. D'Alonzo GE, Nathan RA, Henochoicz S, Morris RJ, Ratner P, Rennard SI. Salmeterol xinafoate as maintenance therapy compared with albuterol in patients with asthma. *JAMA* 1994;271:1412-6.
14. Lipworth BJ, Struthers AD, McDevitt DG. Tachyphylaxis to systemic but not to airway responses during prolonged therapy with high dose inhaled salbutamol in asthmatics. *Am Rev Respir Dis* 1989;140:586-92.
15. Weber RW, Smith JA, Nelson HS. Aerosolized terbutaline in asthmatic development of subsensitivity with long-term administration. *J Allergy Clin Immunol* 1982;70:417-22.
16. Repsher LH, Anderson JA, Bush RK, Falliers CJ, Kass I, Kemp JP, et al. Assessment of tachyphylaxis following prolonged therapy of asthma with inhaled albuterol aerosol. *Chest* 1984;85:34-8.
17. Nelson HS, Raine D Jr, Doner HC, Posey WC. Subsensitivity to the bronchodilator action of albuterol produced by chronic administration. *Am Rev Respir Dis* 1977;116:871-8.
18. Hancox RJ, Cowan JO, Flannery EM, Herbison GP, McLachlan CR, Taylor DR. Bronchodilator tolerance and rebound bronchoconstriction during regular inhaled beta-agonist treatment. *Respir Med* 2000;94:767-71.
19. Wahedna I, Wong CS, Wisniewski AF, Pavord ID, Tattersfield AE. Asthma control during and after cessation of regular beta2-agonist treatment. *Am Rev Respir Dis* 1993;148:707-12.
20. Vathenen AS, Knox AJ, Higgins BG, Britton JR, Tattersfield AE. Rebound increase in bronchial responsiveness after treatment with inhaled terbutaline. *Lancet* 1988;1:554-8.
21. van Schayck CP, Graafma SJ, Visch MB, Dompeling E, van Weel C, van Herwaarden CL. Increased bronchial responsiveness after inhaling salbutamol during 1 year is not caused by subsensitization to salbutamol. *J Allergy Clin Immunol* 1990;86:793-800.

22. van Schayck CP, Cloosterman SG, Bijl-Hofland ID, van den Hoogen H, Folgering HT, van Weel C. Is the increase in bronchial responsiveness or FEV1 shortly after cessation of beta2-agonist reflecting a real deterioration of the disease in allergic asthmatic patients? A comparison between short-acting and long-acting beta2-agonists. *Respir Med* 2002;96:155-62.
23. Inman MD, O'Byrne PM. The effect of regular inhaled albuterol on exercise-induced bronchoconstriction. *Am J Respir Crit Care Med* 1996;153:65-9.
24. Cockcroft DW, McParland CP, Britto SA, Swystun VA, Rutherford BC. Regular inhaled salbutamol and airway responsiveness to allergen. *Lancet* 1993;342:833-7.
25. Cockcroft DW, O'Byrne PM, Swystun VA, Bhagat R. Regular use of inhaled albuterol and the allergen-induced late asthmatic response. *J Allergy Clin Immunol* 1995;96:44-9.
26. Gauvreau GM, Jordana M, Watson RM, Cockcroft DW, O'Byrne PM. Effect of regular inhaled albuterol on allergen-induced late responses and sputum eosinophils in asthmatic subjects. *Am J Respir Crit Care Med* 1997;156:1738-45.
27. Cockcroft DW, Swystun VA, Bhagat R. Interaction of inhaled β_2 agonist and inhaled corticosteroid on airway responsiveness to allergen and methacholine. *Am J Respir Crit Care Med* 1995;152:1485-9.
28. Bhagat R, Swystun VA, Cockcroft DW. Salbutamol-induced increased airways responsiveness to allergen and reduced protection versus methacholine: dose response. *J Allergy Clin Immunol* 1996;97:47-52.
29. Au DH, Lemaitre RN, Curtis JR, Smith NL, Peaty BM. The risk of myocardial infarction associated with inhaled beta-adrenoceptor agonists. *Am J Respir Crit Care Med* 2000;161:827-30.
30. Suissa S, Assimes T, Ernst P. Inhaled short acting beta-agonist use in COPD and the risk of acute myocardial infarction. *Thorax* 2003;58:43-6.
31. Suissa S, Hemmelgard B, Blais L, Ernst P. Bronchodilators and acute cardiac death. *Am J Respir Crit Care Med* 1996;154:1598-602.
32. Au DH, Udris EM, Curtis JR, McDonnell MD, Fihn SD, the ACQUIP investigators. Association between chronic heart failure and inhaled B2-adrenoceptor agonists. *Am Heart J* 2004;148:915-20.
33. Poller U, Fuchs B, Gorf A, Jakubetz J, Radke J, Poniekie K, et al. Terbutaline-induced desensitization of human cardiac B2-adrenoceptor-mediated positive inotropic effects, attenuation by ketotifen. *Cardiovasc Res* 1998;40:211-22.
34. Sengstock DM, Obeidat O, Pasnoori V, Mehra P, Sandberg KR, McCullough PA. Asthma, B-agonists and development of Congestive heart failure: results of the ABCHF study. *J Card Fail* 2002;8:232-8.
35. Taylor DR, Town GI, Herbison GP, Boothman-Burell D, Flannery EM, Hancox B, et al. Asthma control during long-term treatment with regular inhaled salbutamol and salmeterol. *Thorax* 1998;53:748-52.
36. Israel E, Drazen JM, Liggett SB, Boushey HA, Cherniack RM, Chinchilli VM, et al. The effect of polymorphisms of the b2 adrenergic receptor on the response to regular use of albuterol in asthma. *Am J Respir Crit Care Med* 2000;162:75-80.
37. Israel E, Chinchilli VM, Ford JG, Boushey HA, Cherniack R, Craig TJ, et al. Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomized, placebo-controlled cross-over trial. *Lancet* 2004;364:1505-12.
38. Taylor DR, Drazen JM, Herbison GP, Yandava CN, Hancox RJ, Town GI. Asthma exacerbations during long term β agonist use: influence of β_2 adrenoceptor polymorphism. *Thorax* 2000;55:762-7.
39. Johnson M, Butchers Pr, Colman RA, Nials AT, Strong P, Sumner MS, et al. The pharmacology of salmeterol. *Life Sci* 1993;52:2131-43.
40. Anderson GP. Formoterol: pharmacology, molecular basis of agonism, and mechanism of long duration of a highly potent and selective β_2 adrenoceptor agonist bronchodilator. *Life Sci* 1993;52:2145-60.
41. Fitzgerald JM, Chapman KR, Della Cioppa G, Stubbing D, Fairbairn MS, Till D. Sustained bronchoprotection, bronchodilation, and symptom control during regular formoterol use in asthma of moderate or greater severity. *J Allergy Clin Immunol* 1999;103:427-34.
42. Bensch G, Lapidus RJ, Levine BE, Lumry W, Yegen U, Kiselev P, et al. A randomized, 12-week, double-blind, placebo-controlled study comparing formoterol dry powder inhaler with albuterol metered-dose inhaler. *Ann Allergy Asthma Immunol* 2001;86:19-27.
43. Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). *BMJ* 2000;320:1368-73.
44. O'Byrne PM, Barnes PJ, Rodriguez-Rotsin R, Runnerstrom R, Sandstrom T, Svensson K, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. *Am J Respir Crit Care Med* 2001;164:1192-7.
45. Nelson HS, Chapman KR, Pyke SD, Johnson M, Pritchard JN. Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers. *J Allergy Clin Immunol* 2003;112:29-36.
46. Stoloff SW, Stempel DA, Mayer J, Stanford RH, Rosenzweig JRC. Improved refill persistence with fluticasone propionate and salmeterol in a single inhaler compared with other controller therapies. *J Allergy Clin Immunol* 2004;113:245-51.
47. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJH, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The gaining optimal asthma control study. *Am J Respir Crit Care Med* 2004;170:836-44.
48. Pauwels R, Lofdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET). *N Engl J Med* 1998;338:1405-11.
49. Fitzgerald JM, Chapman KR, Della Cioppa GB, Stubbing D, Fairbairn MS, Till MD, et al. Sustained bronchoprotection, bronchodilation and symptom control during regular formoterol use in asthma of moderate or greater severity. *J Allergy Clin Immunol* 1999;103:427-35.
50. Bensch G, Lapidus RJ, Levine BE, Lumry W, Yegen U, Kiselev P, et al. randomized, 12-week, double-blind placebo-controlled study comparing formoterol dry powder inhaler with albuterol metered-dose inhaler. *Ann Allergy Asthma Immunol* 2001;86:19-27.
51. Newnham DM, Grove A, McDevitt DG, Lipworth BJ. Subsensitization of bronchodilator and systemic beta-2 adrenoceptor responses after regular twice-daily treatment with eformoterol dry powder in asthmatic patients. *Thorax* 1995;50:475-504.
52. Britton MG, Earnshaw JS, Palmer JBD. A twelve month comparison of salmeterol with salbutamol in asthmatic patients. *Eur Respir J* 1992;5:1062-7.
53. van der Woude HJ, Winter TH, Aalbers R. Decreased bronchodilating effect of salbutamol in relieving methacholine induced moderate to severe bronchoconstriction during high dose treatment with long acting β_2 agonists. *Thorax* 2001;56:529-35.
54. Jones SL, Cowan JO, Flannery EM, Hancox RJ, Herbison GP, Taylor DR. Reversing acute bronchoconstriction in asthma: the effect of bronchodilator tolerance after treatment with formoterol. *Eur Respir J* 2001;17:368-73.
55. Haney S, Hancox. Rapid onset of tolerance to beta-agonist bronchodilation. *Respir Med* 2005;99:566-71.
56. Grove A, Lipworth BJ. Bronchodilator subsensitivity to salbutamol after twice daily salmeterol in asthmatic patients. *Lancet* 1995;348:201-6.
57. Nelson HS, Berkowitz RB, Tinkelman DA, Emmett AH, Rickard KA, Yancey SW. Lack of subsensitivity to albuterol after treatment with salmeterol in patients with asthma. *Am J Respir Crit Care Med* 1999;159:1556-61.
58. Langley SJ, Masterson CM, Batty EF, Woodcock A. Bronchodilator response to salbutamol after chronic dosing with salmeterol or placebo. *Eur Respir J* 1998;11:1081-5.
59. Korosec M, Novak RD, Myers E, Skowronski M, McFadden ER Jr. Salmeterol does not compromise the bronchodilator response to albuterol during acute episodes of asthma. *Am J Med* 1999;107:209-13.
60. Ullman A, Hedner J, Svedmyr N. Inhaled salmeterol and salbutamol in asthmatic patients. *Am Rev Respir Dis* 1990;142:571-5.
61. Yates DH, Sussman HS, Shaw MJ, Barnes PJ, Chung KF. Regular formoterol treatment in mild asthma: effect on bronchial responsiveness during and after treatment. *Am J Respir Crit Care Med* 1995;152:1170-4.
62. Booth H, Fishwick K, Harkawat R, Devereux G, Hendrick DJ, Walters EH. Changes in methacholine induced bronchoconstriction with the long acting β_2 agonist salmeterol in mild to moderate asthmatic patients. *Thorax* 1993;48:1121-4.
63. Boulet L-P, Chakir J, Milot J, Boutet M, Laviolette M. Effect of salmeterol on allergen-induced airway inflammation in mild allergic asthma. *Clin Exp Allergy* 2001;31:430-7.
64. Cheung D, Timmers MC, Zwinderman AH, Bel EH, Dijkman JH, Sterk PJ. long-term effects of a long-acting β_2 adrenoceptor agonist,

- salmeterol, on airway hyperresponsiveness in patients with mild asthma. *N Engl J Med* 1992;327:1196-203.
65. Kalra S, Swystun VA, Bhagat R, Cockcroft DW. Inhaled corticosteroids do not prevent the development of tolerance to the bronchoprotective effect of salmeterol. *Chest* 1996;109:953-6.
 66. Ramage L, Lipworth BJ, Ingram CG, Cree IA, Dhillon DP. Reduce protection against exercise induced bronchoconstriction after chronic dosing with salmeterol. *Respir Med* 1994;88:363-8.
 67. Garcia R, Guera P, Feo F, Galindo PA, Gomez E, Borja J. Tachyphylaxis following regular use of formoterol in exercise-induced bronchospasm. *J Invest Allergol Clin Immunol* 2001;11:176-82.
 68. Simons FE, Gerstner TV, Cheung MS. Tolerance to the bronchoprotective effects of salmeterol in adolescent with exercise-induced asthma using concurrent inhaled glucocorticoid treatment. *Pediatrics* 1997;99:655-9.
 69. Edelman JM, Turin JA, Bronsky EA, Grossman J, Kemp JP, Ghannam AT, et al. Oral montelukast compared with inhaled salmeterol to prevent exercise-induced bronchoconstriction. *Ann Intern Med* 2000;132:97-104.
 70. Burgess C, Ayson M, Rajasingham S, Crane J, Della Cioppa G, Till MD. The extrapulmonary effects of increasing doses of formoterol in patients with asthma. *Eur J Clin Pharmacol* 1998;54:141-7.
 71. Ferguson GT, Funck-Brentano C, Fischer T, Darken P, Reisner C. Cardiovascular safety of salmeterol in COPD. *Chest* 2003;123:1817-24.
 72. Martin RM, Dunn NR, Freemantle SN, Mann RD. Risk of non-fatal cardiac failure and ischemic heart disease with long-acting beta₂ agonists. *Thorax* 1998;53:558-72.
 73. Dorinsky PM, Yancey S, Baitinger L, Edwards L, Sutton L, Klotzman M, et al. Salmeterol response is not effected by beta₂-adrenergic receptor genotype in patients with persistent asthma. *Chest* 2004;126(suppl):722S.
 74. Dorinsky P, Yancey S, Edwards L, Sutton L, Ortega H. Rates of asthma exacerbations are not effected by beta₂-adrenergic receptor genotype in patients with persistent asthma. *J Allergy Clin Immunol* 2005;115(suppl 1):S6.
 75. Kraft M, Wenzel SE, Betting CM, Martin RJ. The effect of salmeterol on nocturnal symptoms, airway function and inflammation in asthma. *Chest* 1997;111:1249-54.
 76. Roberts JA, Bradding P, Britten KM, Walls AF, Wilson S, Gratziau C, et al. The long-acting beta₂-agonist salmeterol xinafoate: effects on airway inflammation in asthma. *Eur Respir J* 1999;14:275-82.
 77. Orsida BE, Ward C, Li X, Bish R, Wilson JW, Thien F, et al. Effect of a long-acting β_2 agonist over three months on airway wall vascular remodeling in asthma. *Am J Respir Crit Care Med* 2001;164:117-21.
 78. Wallin A, Sandstrom T, Soderberg M, Howarth P, Lundback B, Della-Cioppa G, et al. The effect of regular inhaled formoterol, budesonide, and placebo on mucosal inflammation and clinical indices in mild asthma. *Am J Respir Crit Care Med* 1999;159:79-86.
 79. Jeffery PK, Venge P, Gzycki MJ, Egerod I, Dahl R, Faourschou P. Effects of salmeterol on mucosal inflammation in asthma: a placebo-controlled study. *Eur Respir J* 2002;20:1378-85.
 80. Kips JC, O'Connor BJ, Inman MD, Svensson K, Pauwels RA, O'Byrne PM. A long-term study of the anti-inflammatory effect of low-dose budesonide plus formoterol versus high-dose budesonide in asthma. *Am J Respir Crit Care Med* 2000;161:996-1001.
 81. Li X, Ward C, Thien F, Bish R, Bamford T, Bao X, et al. An anti-inflammatory effect of salmeterol, a long-acting beta₂ agonist, assessed in airway biopsies and bronchoalveolar lavage in asthma. *Am J Respir Crit Care Med* 1999;160:1493-9.
 82. Wallin AM, Sue-Chu M, Bjerner I, Ward J, Sandstrom T, Lindberg A, et al. Effect of inhaled fluticasone with and without salmeterol on airway inflammation in asthma. *J Allergy Clin Immunol* 2003;112:72-8.
 83. National Institutes of Health, National Heart, Lung and Blood Institute. Guidelines for the diagnosis and management of asthma: update on selected topics 2002. *J Allergy Clin Immunol* 2002;110(suppl):S141-219.
 84. Lazarus SC, Boushey HA, Fahy JV, Chinchilli VM, Lemanske RF Jr, Sorkness CA, et al. Long-acting B₂-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. *JAMA* 2001;285:2583-93.
 85. Simons FE. A comparison of beclomethasone, salmeterol and placebo in children with asthma. *N Engl J Med* 1997;337:1659-65.
 86. Verberne AA, Frost C, Roorda RJ, van der Laag H, Kerrebijn KF. One year treatment with salmeterol. Compared with beclomethasone in children with asthma. *Am J Respir Crit Care Med* 1997;156:688-95.
 87. McIvor RA, Pizzichini E, Turner MO, Hussack P, Hargreave FE, Sears MR. Potential masking effects of salmeterol on airway inflammation in asthma. *Am J Respir Crit Care Med* 1998;158:924-30.
 88. Campbell DA, McLennan G, Coates JR, Frith PA, Gluyas PA, Latimer KM, et al. A comparison of asthma deaths and near-fatal asthma attack in South Australia. *Eur Respir J* 1994;7:490-7.
 89. Matz J, Emmett A, Rickard K, Kalberg C. Addition of salmeterol to low-dose fluticasone versus higher-dose fluticasone: an analysis of asthma exacerbations. *J Allergy Clin Immunol* 2001;107:783-9.
 90. Pace E, Gagliardo R, Melis M, La Grutta S, Ferraro M, Siena L, et al. Synergistic effects of fluticasone propionate and salmeterol on in vitro T-cell activation and apoptosis in asthma. *J Allergy Clin Immunol* 2004;114:1216-23.
 91. Baraniuk J, Ali M, Brody D, Maniscalco J, Gaumond E, Fitzgerald T, et al. Glucocorticoids induce beta₂-adrenergic receptor function in human nasal mucosa. *Am J Respir Crit Care Med* 1997;155:704-10.
 92. Eickelberg O, Roth M, Lox R, Bruce V, Rudiger J, Johnson M, et al. Ligand-independent activation of glucocorticoid receptor by beta₂-adrenergic receptor agonists in primary human lung fibroblasts and vascular smooth muscle cells. *J Biol Chem* 1999;274:1005-10.
 93. Wilkinson JR, Roberts JA, Bradding P, Holgate ST, Howarth PH. Paradoxical bronchoconstriction in asthmatic patients after salmeterol by metered dose inhaled. *BJM* 1992;305:931-2.
 94. Clark CE, Ferguson AD, Siddorn JA. Respiratory arrests in young asthmatics on salmeterol. *Respir Med* 1993;87:227-8.
 95. Finkelstein FN. Risks of salmeterol. *N Engl J Med* 1994;331:1314.
 96. Mann RD, Kubota K, Pearce G, Wilton L. Salmeterol: a study by prescription-event monitoring in a UK cohort of 15,407 patients. *J Clin Epidemiol* 1996;49:247-50.
 97. Williams C, Crossland L, Finnerty J, Crane J, Holgate S, Pearce N, et al. Case-control study of salmeterol and near-fatal attacks of asthma. *Thorax* 1998;53:7-13.
 98. Lanes SF, Lanza LL, Wentworth CE III. Risk of emergency care, hospitalization, and ICU stays for acute asthma among recipients of salmeterol. *Am J Respir Crit Care Med* 1998;158:857-61.
 99. Meier CR, Jick H. Drug use and pulmonary death rates in increasingly symptomatic asthma patients in the UK. *Thorax* 1997;52:612-7.
 100. Anderson HR, Ayres JG, Sturdy PM, Bland JM, Butland BK, Peckitt C, et al. Bronchodilator treatment and deaths from asthma: case-control study. *BMJ* 2005;330:117.
 101. Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *BMJ* 1993;306:1034-7.
 102. Mann M, Chowdhury B, Sullivan E, Nicklas R, Anthracite R, Meyer RJ. Serious asthma exacerbations in asthmatics treated with high-dose formoterol. *Chest* 2003;124:70-4.
 103. Wolfe J, LaForce C, Ziehmer B, Orevillo C, Till D. High-dose formoterol not associated with increased asthma exacerbations. *Proc Am Thorac Soc* 2005;2:A128.
 104. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The salmeterol multicenter asthma research trial (SMART): a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest*; in press.