Inhaled Corticosteroids and LABAs — Removal of the FDA's Boxed Warning

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For years, the risks associated with the use of long-acting beta-agonists (LABAs) in patients with asthma have been uncertain, and some health care professionals have recommended conducting large clinical trials to gather important safety information on these products.[1] In December 2017, the Food and Drug Administration (FDA) removed the boxed warning on combination products containing an inhaled corticosteroid and a LABA on the basis of results from recently completed large safety trials that the agency required manufacturers to conduct. Removal of a boxed warning isn't common, but we at the FDA believe that the data generated from the mandated trials support this regulatory action. The findings also improve the knowledge base for clinicians who treat patients with asthma.

The boxed warning was initially required in 2003 on the basis of findings that suggested LABAs were associated with serious adverse outcomes, including asthma-related hospitalization, intubation, and death. The main investigations that raised those concerns, the Salmeterol Nationwide Surveillance Study and the Salmeterol Multicenter Asthma Research Trial, were conducted at a time when patients taking LABAs were not necessarily using inhaled corticosteroids as well. It was therefore unknown whether use of an inhaled corticosteroid in combination with a LABA — now considered the standard of care — would mitigate the risk of serious asthma outcomes. Consequently, the FDA required the boxed warning for LABAs and combination products.

Given continued concerns regarding the use of LABAs, and in particular the risk of asthma-related hospitalizations among children, in 2011 the FDA required manufacturers to conduct clinical trials evaluating the safety of combination products as compared with inhaled corticosteroids alone.[2] Five clinical trials were required: four in adults and adolescents 12 years of age or older and one in children 4 to 11 years of age. The trials were randomized and double-blinded and lasted 6 months. Enrolled patients had a history of at least one asthma exacerbation in the previous 12 months and were thought to be at risk for additional exacerbations but not to have unstable or life-threatening asthma. The primary safety end point was a composite of serious asthma outcomes, including asthma-related death, intubation, or hospitalization.

The individual adult and adolescent trials had noninferiority designs; a sample size of 11,700 provided 90% power to rule out a doubling of risk in each trial. These trials shared joint independent steering, adjudication, and data monitoring committees so the results could be combined and investigators could evaluate the incidence of rare events, such as asthma-related death and intubation. The pediatric trial was similar in design to the adult and adolescent trials and had the same primary end point; however, the sample size was 6200, which provided 90% power to rule out a 2.7-fold increase in risk. An independent, blinded adjudication committee determined whether the adverse events in question were likely to be related to asthma.

Four of the trials were completed, whereas one of the adult and adolescent trials was terminated early when Novartis discontinued marketing of formoterol fumarate (Foradil Aerolizer) in the United States (NCT01462344, NCT01475721, NCT01471340, NCT01444430, and NCT01845025). Each completed trial met the prespecified objective and demonstrated noninferiority of combination products to inhaled corticosteroids alone with respect to the composite end point of asthma-related death, intubation, or hospitalization. The majority of events were asthma-related hospitalizations; there were five intubations and deaths overall.

We combined data from the three completed adult and adolescent trials (we chose not to include data from the pediatric trial; these results were analyzed separately to address specific concerns in this age group). The original objective for combining these data was to evaluate rates of

Rate of Serious Asthma Outcomes in Patients Taking Combination Products versus Inhaled Corticosteroids Alone.*

Study	Inhaled Corticosteroid and LABA	Inhaled Corticosteroid	Hazard Ratio (95% CI)
	no./total no. (%)		
Adult and adolescent			
Advair (fluticasone and salmeterol)	34/5834 (0.58)	33/5845 (0.56)	1.03 (0.64–1.66)
Symbicort (budesonide and formoterol)	43/5838 (0.74)	40/5843 (0.68)	1.07 (0.70–1.65)
Dulera (mometasone and formoterol)	39/5865 (0.66)	32/5864 (0.55)	1.22 (0.76–1.94)
Combined analysis	116/17,537 (0.66)	105/17,552 (0.60)	1.10 (0.85–1.44)
Pediatric			
Advair (fluticasone and salmeterol)	27/3107 (0.87)	21/3101 (0.68)	1.29 (0.73–2.28)

* A serious asthma outcome was defined as hospitalization, intubation, or death. Only participants who took at least one dose of the assigned treatment were included. The hazard ratios and 95% confidence intervals (CIs) for the meta-analysis were calculated by fitting a Cox model stratified by trial using a single covariate of planned treatment group. Noninferiority margins were 2.0 for the adult and adolescent trials and 2.7 for the pediatric trial. LABA denotes long-acting beta-agonist. The differences between this table and the data in the article by Busse et al.[3] reflect assumptions made concerning the makeup of the analysis populations.

death and intubation, but given the small number of events, we focused instead on the composite end point. Our analyses showed no significant increase in the risk of serious asthma-related events associated with combination products containing an inhaled corticosteroid and a LABA as compared with inhaled corticosteroids alone (hazard ratio, 1.10; 95% confidence interval [CI], 0.85 to 1.44) (see table). The results were consistent across subgroups of interest, including U.S. blacks (hazard ratio, 0.95; 95% CI, 0.48 to 1.90), women (hazard ratio, 1.18; 95% CI, 0.86 to 1.61), and people 65 years of age or older (hazard ratio, 0.85; 95% CI, 0.45 to 1.60).

Efficacy was also assessed. The primary efficacy measure was the rate of asthma exacerbations, defined as an asthma deterioration that required use of systemic corticosteroids for at least 3 days, inpatient hospitalization, or an emergency department visit that also involved use of systemic corticosteroids. Each adult and adolescent trial demonstrated a significant reduction in predefined asthma exacerbations among patients treated with combination products as compared with patients treated with inhaled corticosteroids alone. The majority of asthma exacerbations were deteriorations that required systemic steroids, rather than hospitalizations or emergency department visits.

The individual trials all met the primary safety objective, and results were consistent among trials. In addition, the observed reduction in asthma exacerbations that required systemic corticosteroids demonstrates a benefit associated with combination products. On the basis of this strong and consistent evidence, we opted to remove the boxed warning right away, without convening an FDA advisory-committee meeting.

Admittedly, the results from these trials cannot answer all questions regarding the safety of LABAs. Some uncertainties remain, and we cannot conclude that there is no increase in risk associated with combination products containing an inhaled corticosteroid and a LABA as compared with inhaled corticosteroids alone. Although the trials found that combination therapy reduces the rate of exacerbations that require the administration of systemic corticosteroids, none of them showed a decrease in asthma-related hospitalizations. People with life-threatening asthma were excluded because of safety and ethical concerns, so we don't know whether the results can be generalized to these patients.[4] Finally, although the pediatric trial met the primary safety objective, the noninferiority margin was, for reasons of trial feasibility, larger than ideal. Despite these uncertainties and limitations, the trials provided reassuring safety information and demonstrated additional benefits associated with combination therapy.

Our conclusion based on the data generated from these trials is that there is not a significant increase in the risk of serious

asthma-related events associated with combination therapy as compared with inhaled corticosteroids alone. The FDA's decision to remove the boxed warning from combination products was based on our assessment of data from FDA-required trials. Any FDA mandate for large safety trials should be predicated on science and patient welfare and established for the purpose of answering important safety questions to improve health care providers' knowledge and patient care. The removal of a boxed warning from a product label is not a common occurrence, but the evidence in this instance was decisive.

Disclosure forms provided by the authors are available at NEJM.org.

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1. Drazen JM, O'Byrne PM. Risks of long-acting beta-agonists in achieving asthma control. N Engl J Med 2009;360:1671-2.
2. Chowdhury BA, Seymour SM, Levenson MS. Assessing the safety of adding LABAs to inhaled corticosteroids for treating asthma. N Engl J Med 2011;364:2473-5.
3. Busse WW, Bateman ED, Caplan AL, et al. Combined analysis of asthma safety trials of long-acting β_2-agonists. N Engl J Med 2018; 378:2497-505.
4. Martinez FD. Safety of fluticasone plus salmeterol in asthma — reassuring data, but no final answer. N Engl J Med 2016;374: 1887-8.

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