What are the risks of long-acting beta-agonist (LABA) use in patients with asthma?

Evidence-Based Answer
This answer remains uncertain and controversial. Two recent meta-analyses have conflicting results. One found an increased risk of asthma-related intubation and death when LABAs are used alone or in combination with inhaled corticosteroids (ICS). A second systematic review found improved asthma-related outcomes when adding LABAs to ICS in adult patients with inadequately controlled asthma. These reviews differed in their primary endpoints and inclusion criteria.

The results of The Salmeterol Multicenter Asthma Research Trial (SMART) were published in 2006 with an interim analysis of 26,355 subjects older than 12 years.\(^1\) This trial was a 28-week, randomized, double-blind, placebo-controlled, observational study. Participants were randomized to salmeterol or placebo in addition to any chronic asthma medication already being used. At baseline, the African American subgroup had greater asthma disease severity than Caucasians. Only 47% of participants were using ICS.

No significant difference was noted in the primary combined endpoint of respiratory-related deaths and life-threatening events. Among secondary endpoints, salmeterol use was associated with an increase in respiratory-related death (RR=2.16; 95% CI, 1.06–4.41), asthma-related death (RR=4.37; 95% CI, 1.25–15.34), and combined asthma-related deaths and life-threatening events (RR=1.71; 95% CI, 1.01–2.89) versus placebo. This increased risk was largely noted in the African American subpopulation. The study was terminated at interim analysis without meeting predefined criteria.\(^1\)

A meta-analysis of 36,588 participants (including SMART) was published in 2010 examining the effects of the addition of LABA to other medications for treatment of chronic asthma.\(^2\) Primary endpoints were asthma-related intubation and death. Studies were included if they were RCTs of at least 3 months’ duration and reported at least 1 asthma-related intubation or death.

In the consistent-use ICS subgroup, adding LABA was associated with a significant increase in catastrophic events compared with controls (OR 1.83; 95% CI, 1.14–2.95). For the entire meta-analysis, only 12 (10 individual trials and 2 pooled trials from GlaxoSmithKline) of 211 potentially relevant studies met inclusion criteria and 83 were excluded, because they reported no adverse events. The authors noted the results were based on a small number of events and should be interpreted with caution.\(^2\)

A 2010 Cochrane systematic review included 48 studies and 15,155 patients, mostly adults, to evaluate the addition of LABA to ICS versus increased ICS dose.\(^3\) The primary endpoint was asthma exacerbations requiring systemic corticosteroids. Inclusion criteria were RCTs comparing LABA and ICS with higher dose ICS in children and adults with asthma. Participants had generally moderate airway obstruction.

Combination therapy resulted in significantly lower risk of exacerbations requiring systemic corticosteroids (RR=0.88; 95% CI, 0.78–0.98). The NNT to prevent 1 asthma exacerbation was 73. No statistically significant difference was noted in risk ratios for serious adverse events (RR=1.12; 95% CI, 0.91–1.37), which was a secondary endpoint.\(^3\)

Further research is required to evaluate the risks and benefits of LABA addition to ICS. The Cochrane review provides detailed recommendations on study endpoints and design for future investigation.

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