Several studies suggested an association between the regular use of β2-agonists and asthma deaths. [1] In particular, one postmarketing surveillance study of salmeterol [2] showed a three-fold increase in deaths in the salmeterol group compared with the placebo group, but the difference was not significant as the rate of "events" was low and not different from what was expected. In 1996, due to reports of paradoxical bronchospasm and, moreover, the documented non significant increased risk of asthma-related death [2] associated with the use of salmeterol and previous epidemics of asthma-related deaths in patients taking other β2-agonists, [3] the Salmeterol Multicenter Asthma Research Trial (SMART) was designed in order to further evaluate the effects of salmeterol on respiratory- and asthma-related deaths or life-threatening episodes. A total of 26,353 patients completed the study, of which 13,174 had received salmeterol and 13,179 placebo. [4]

There was no significant difference in combined number of respiratory related deaths or life-threatening experiences (intubation and ventilation), which was the primary outcome (salmeterol=48; placebo=42) or in time to onset of the primary event. No significant differences were seen between salmeterol and placebo in the incidence of any secondary endpoint (asthma-related deaths and combined asthma related deaths or life-threatening experiences), with the exception of asthma-related death which occurred rarely and was significantly higher in salmeterol vs placebo (13 vs 3). It must be highlighted that bronchial asthma was the cause of death in only 5 out of 16 reported deaths. [4]

Intriguingly, African-American patients receiving salmeterol experienced a higher incidence of asthma-related deaths vs placebo (8 vs 1); no difference in Caucasians (5 vs 2).

Asthma-related death was lower in inhaled corticosteroid (ICS) users vs non-ICS users regardless of treatment, and asthma-related deaths occurred more frequently in salmeterol who did not use ICS. [4] Similar results occurred in Caucasians and African-Americans. [4]

A critical assessment of the results of the SMART clearly shows that, in contrast to recommendations of current asthma management guidelines, [5] there was a low level of ICS use (47%) in the entire population in the SMART. Only 50% of Caucasian patients were receiving treatment with an ICS, and in African-American patients, who had more severe asthma at entry, only 38% were using ICS therapy at baseline.

Although there was no attempt to determine degree of adherence with ICS at randomisation or persistence in their use during the course of the study, no significant differences were seen for primary events and asthma-related events, including deaths in the total population of patients receiving ICS at baseline. However, in the total population of patients not receiving ICS at baseline, there was a statistically significant greater number of asthma-related deaths in all patients taking salmeterol compared with those taking placebo.

Another crucial point is the documentation that in Caucasian patients (71% of the study population) there were no significant differences between treatment groups for primary events and asthma-related events. In African-American participants (17% of the study population), the study showed a statistically significant greater number of asthma-related deaths in all patients taking salmeterol compared with those taking placebo.

It is likely that the lower level of ICS use may have contributed to the higher rate of asthma related events among African-Americans. In any case, it must be highlighted that the study was not sufficiently powered a priori to evaluate properly post hoc subgroup analysis for the effects of ICS use or ethnic origin, but indicated that the risks were greater in African Americans who were using ICS less frequently. [6]
Despite all of the concerns raised by the SMART and a recent meta-analysis of the effect of long-acting β-agonists (LABAs) on severe asthma exacerbations and asthma-related deaths, [7] which documented that LABA use increases the risk for hospitalisations due to asthma, life-threatening asthma exacerbations, and asthma-related deaths with similar risks found with salmeterol and formoterol and in children and adults, inhaled β2-agonists remain the most effective bronchodilators available for the immediate relief of asthma symptoms and, as such, remain an important component of asthma management. [8]

Obviously, there are concerns about LABA treatment as monotherapy for asthma, and Asthma Guideline recommendations [5] emphasise the need for adequate anti-inflammatory therapy before starting any add-on treatment, including LABAs. Patients with asthma should be initiated and maintained on sufficiently high doses of ICSs and only patients whose asthma cannot be controlled should receive additional LABAs on a regular basis.

In effect, there is a large body of evidence documenting that ICSs and LABAs have a separate but complementary role in the management of asthma [Barnes, 2002] and, consequently, LABAs in combination with ICSs are the most effective asthma treatment currently available for the management of asthma. This opinion fits with asthma mortality data in the US. These data document that deaths from asthma peaked in 1996, two years after the introduction of salmeterol in the US, at 5,667 Subsequently, use of salmeterol, largely in combination with fluticasone, has increased 5-fold while deaths from asthma in the US have steadily fallen to 3,780 in 2004. [10]

Therefore, it is premature (and inappropriate) of Martinez [11] and Salpeter et al. [7] to suggest that withdrawal of LABAs should even be considered.

REFERENCES

8 O’Byrne PM, Adelroth E. β2 déjà vu. Chest 2006; 129: 3-5