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The Debate About the Use of Long-Acting Inhaled β_2-agonists in Asthma

Paul M. O'Byrne MB, FRCP(C), FRSC

Firestone Institute for Respiratory Health, St. Joseph's Healthcare and the Department of Medicine, Michael G DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada

ABSTRACT

Long-acting inhaled β_2-agonists (LABAs) have been available for the treatment of asthma for almost 30 years; there is, however, concern about their safety with regular use. There is widespread agreement that LABA should not be used as monotherapy by asthmatic patients, because, while they are very effective in providing symptom relief, they have no inherent anti-inflammatory properties, and may increase the risk of asthma mortality. When used together with inhaled corticosteroids (ICS), ideally in the same inhaler, ICS/LABA combinations have been shown to improve asthma control and reduce risk of asthma exacerbations. Concerns about the risks of severe asthma related events, such as hospitalization, intubation or death, associated with the use of ICS/LABA combinations have been allayed by the results of several recent large randomized safety trials conducted both in adults and children. **(BRN Rev. 2017;3:166-77)**

Corresponding author: Paul M. O'Byrne, obyrnep@mcmaster.ca

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Correspondence to:
Paul M. O'Byrne
Health Science Center, Rm 2E1
1280 Main Street West, Hamilton
Ontario, L8S 4K1, Canada
E-mail: obyrnep@mcmaster.ca

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INTRODUCTION

It was recognized, in the mid 1940's that inhaled epinephrine, when delivered by inhalation, provided relief from bronchoconstriction in asthmatic patients[1]. The first synthetic inhaled catecholamine to be used for the treatment of asthma was isoprenaline, with initial reports of beneficial effects published in 1948[2]. The modern β_2-agonists were developed based on the identification that catecholamines, such as epinephrine, exerted their effects via distinct α- and β-receptors[3]. Subsequently, Lands[4] characterized the β-adrenoceptors into β_1- and β_2-subdivisions, leading to efforts to develop selective agonists for the β_2-receptor in the lungs. β_2-agonist selectivity was improved by modifying the structure of catecholamines, while other modifications extended the duration of action after inhalation. The commonly available short-acting inhaled β_2-agonists (SABAs), such as salbutamol[5] and terbutaline[6], resulted from this initial pharmacological effort.

Several decades later, selective β_2-agonists with longer durations of action were developed, long-acting inhaled β_2-agonists (LABAs). The initial members of this class were salmeterol and formoterol. Salmeterol was developed from salbutamol, modified to attach the drug near the β_2-receptor by extending its aliphatic side-chain[7]. By contrast, formoterol was initially developed as an oral β_2-agonist by Japanese medicinal chemists, and its long duration of activity when inhaled was discovered serendipitously[8]. Although it is most likely that the binding of salbutamol, terbutaline and formoterol is similar to the binding of epinepherine to β_2-receptor, the nature of salmeterol binding remains controversial. The main difference between the two medications is that salmeterol is intrinsically long-acting, whereas the duration of action of formoterol is critically dependent on its route of administration. Formoterol has high lipoid solubility in the airways. This allows for a reservoir effect with slow release from the cell membrane, resulting in a long duration of action, an effect not seen when formoterol is delivered orally[9]. Finally, LABAs with very long durations of efficacy (> 24 hours) such as indacaterol[10], vilanterol[11] and olodaterol[12] have recently been developed (ultra-LABAs).

Important considerations with regard to the pharmacological properties of β_2-agonists are their selectivity, potency and efficacy. Selectivity reflects the ratios of binding affinities to receptors (β_2- versus β_1-receptors) in *in vitro* assays. All currently available inhaled β_2-agonists have excellent selectivity for β_2- versus β_1-receptor-mediated effects. Potency is the molar concentration of medication required to produce a half-maximal effect. Efficacy is the degree of effect observed compared with the maximal possible effect in a system. Full agonists produce a full response, while partial agonists provide a lesser response. However, the efficacy of a medication depends on the system in which it is tested; if receptors are abundant and well-coupled, partial agonists may appear to be full agonists. Isoprenaline is the classic full agonist on the β-receptor, while salbutamol is a partial agonist on human airway smooth muscle *in vitro;* however, the bronchodilator activity of salbutamol in humans is not distinguishable from isoproterenol. Terbutaline and formoterol are almost full agonists, while salmeterol is a partial agonist on human airway smooth muscle.

EFFICACY OF INHALED β_2-AGONISTS

Asthma treatment guidelines recommend rapid onset inhaled β_2-agonists for the relief of airflow obstruction[13]. Inhaled SABAs are the most widely used, acting rapidly (within 5-10 minutes) to reverse airflow obstruction. If the airflow obstruction is not severe, low doses of inhaled SABAs can usually fully reverse it; however, when airflow obstruction is severe, even high doses of inhaled SABAs are usually not fully effective. Activation of the β_2-receptor can decouple it from its transduction pathways, with the potential for loss of responsiveness with repeated use of SABAs. There is, however, very little evidence that this occurs for bronchodilator responses. Thus, even with regular use of a β_2-agonist over one year the magnitude of bronchodilation can be maintained[14], likely because the intracellular mechanisms which result in bronchodilation require activation of only a relatively small fraction of the available β_2-receptors on an airway smooth muscle to evoke a maximal response.

LABAs were introduced for asthma treatment in 1990, and over time have become widely used in both asthma and chronic obstructive pulmonary disease (COPD). In both diseases, LABAs have been used either as monotherapy, or added to inhaled corticosteroid (ICS). Both salmeterol and formoterol, the LABAs available for chronic maintenance treatment in asthma, have been shown in large randomized controlled trials in asthma to provide better clinical outcomes (symptom control, improved lung function, and reduced exacerbations) when added to an ICS, than doubling the dose of ICS[14,15]. Formoterol has a rapid onset of bronchodilation, and is approved for the acute relief of airflow obstruction in many countries, unlike salmeterol, whose onset to peak bronchodilation takes significantly longer than formoterol[16]. More recently, the benefit of ultra-long acting LABAs, such as vilanterol, have been demonstrated when added to an ICS in asthma[11,17], and this combination has been approved for use in many countries, while others are still under clinical development for use in asthma[12,18].

LABAs continue to be recommended as a monotherapy in COPD[19], as they are both safe and effective[20,21]; however, the use of LABAs for the treatment of asthma is now recommended only in combination with ICS, ideally in a single inhaler[13]. Such ICS/LABA combinations provide better asthma control than high doses of ICS alone in patients whose asthma is not well controlled on lower ICS doses[22], and reduce asthma exacerbations. The effect was first demonstrated in the Formoterol and Corticosteroids Establishing Therapy (FACET) study[14], in which the most substantial impact on reducing mild and severe exacerbations in asthma occurred in the group given both increased ICS and formoterol. This benefit has been consistently reproduced in other studies[23,24]. Asthma treatment guidelines recommend low dose ICS/LABA combinations as the preferred treatment if ICS monotherapy is not providing optimal asthma control[13]. If asthma control remains suboptimal, higher doses of ICS/LABA combinations are recommended.

The mechanisms by which ICS/LABA combinations provide superior overall asthma control compared with ICS alone are not well

understood. LABAs stimulate the glucocorticoid receptor and promote its translocation to the nucleus, increasing corticosteroid-mediated gene transcription[25], while corticosteroids increase the transcription of the β_2-receptor gene in the lung[26]. Suggestions that LABAs possessed intrinsic anti-inflammatory properties have been debated, but a systematic review of the effects of LABAs on a wide range of inflammatory indices (induced cell counts, markers of cell activation in sputum, bronchoalveolar lavage fluid, bronchial biopsy specimens and serum, and exhaled nitric oxide) concluded that LABA therapy was neither anti-inflammatory nor pro-inflammatory[27].

SAFETY OF INHALED β_2-AGONISTS

Questions regarding the safety of inhaled β-agonists in asthma go back to a report in 1948 of increased mortality associated with use of nebulized epinephrine[28], a very non-selective β-agonist, with effects on β_1-receptors on the myocardium. Concern become more widespread in the 1960s when England and Wales, Australia and New Zealand experienced an increase in asthma mortality among young people, associated in time with introduction of a high dose formulation of another non-selective β-agonist, isoprenaline[29]. A further epidemic of asthma mortality occurred in New Zealand from 1976 through the 1980's. Case-control studies suggested a relationship to prescription of fenoterol[30], a more potent and slightly longer acting beta-agonist than salbutamol. These concerns were increased by the findings of a randomized placebo-controlled clinical trial which demonstrated that regular use of fenoterol could increase asthma severity despite concomitant use of ICS[31]. Asthma mortality in New Zealand decreased abruptly when fenoterol was severely restricted, just as mortality in the UK, Australia and New Zealand had decreased in the late 1960's when use of high dose isoprenaline was discouraged. It was also recognized that SABAs do not have any inherent anti-inflammatory activity in asthma, and indeed, in some circumstances, may increase early and late allergen-induced asthmatic responses[32] and promote eosinophilic airway inflammation[33]. SABAs are no longer recommended for regular use in asthma[13], but remain the mainstay of rescue therapy, and the most widely used inhaled medication for asthma.

In part because of the concerns raised by the regular use if SABAs, after the launch of the LABA, salmeterol, in the United Kingdom, Castle et al.[34] conducted a trial comparing twice daily salmeterol with salbutamol four times daily in subjects considered requiring regular β_2-agonist therapy. While exacerbations did not differ, and study discontinuations decreased with salmeterol treatment, there was a disturbing, albeit non-significant, three-fold increase in the risk of mortality in the salmeterol group. The authors considered lack of adequate ICS a likely contributor to many of the 14 deaths.

Because of these concerning, but inconclusive, findings, a large study of salmeterol versus placebo added to usual therapy was conducted in the United States, powered on death as the primary outcome[35]. The study was terminated prematurely, in part because of preliminary findings of a higher proportion of deaths

and serious adverse events with salmeterol. The odds ratio for respiratory-related deaths was 2.16, and for asthma related deaths was 4.37. African Americans in this study appeared to be at higher risk, and the question arose regarding the possible impact of β-receptor genotype, as African Americans have a higher prevalence of Argenine (Arg)-Arg at position 16 of the beta-receptor. However, the apparent higher risk in African Americans largely reflected their higher baseline risk of mortality, as the actual mortality rates in the study in African-Americans and Caucasians were similarly increased, being about 4-fold and 3-fold higher respectively than that expected in relation to their age- and race-matched population. ICS use was not recorded throughout the study, but at baseline, only 38% of African Americans and 49% of Caucasians had been prescribed ICS. *Post hoc* analysis showed that deaths were dominantly among those not prescribed ICS at baseline; among those not using ICS at baseline, there were 9 deaths in the salmeterol arm and none in the placebo arm, whereas among those using ICS at baseline, no difference was seen in the risk of mortality (4 versus 3 deaths).

The concern that inflammation might increase because of insufficient ICS, while concomitant LABA maintained apparent control of asthma, was highlighted by a study demonstrating that salmeterol can mask the clinical effects of inflammation by controlling symptoms and maintaining stable lung function as the sputum eosinophil count increased during steroid reduction[36].

The results of the large US study of salmeterol reported by Nelson et al.[35] led the Food and Drug Administration (FDA) to impose a 'black-box' warning on all products containing salmeterol or formoterol, both as monotherapy and in combination with ICS. This action, and the safety concerns leading to it, resulted in a number of meta-analyses examining safety of LABA therapy in asthma. Salpeter et al.[37] assessed the effect of LABAs on severe asthma exacerbations requiring hospitalization, life-threatening asthma attacks, and asthma-related deaths in adults and children. Randomized, placebo-controlled asthma trials of LABAs with duration of more than 3 months were included, but those without placebo control groups were excluded. The odds ratio for asthma-related deaths for LABA compared to placebo was 3.5 (95% CI: 1.3-9.3). Major criticisms of this meta-analysis were that some 80% of the subjects included were participants in the single study of Nelson et al.[35], exclusion of pivotal studies on the addition of LABAs to ICS because these studies did not have a placebo controlled arm, and the lack of verification of concomitant use of ICS during therapy with LABAs. Ernst et al. compared the analysis of Salpeter et al. with those reported in previous Cochrane reviews, and took the contrary view that LABA used with ICS was safe[38].

Safety data relating to formoterol exposure in clinical trials were subsequently examined by Sears et al.[30]. Asthma-related deaths were 0.34 per 1,000 patient-years among formoterol-randomized patients (92% using ICS) and 0.22 per 1,000 patient-years among patients not randomized to formoterol (83% using ICS) (risk-ratio: 1.57). Asthma-related serious adverse events (SAEs), over 90% of which were hospitalizations, were significantly lower among formoterol-randomized patients. There was

no increase in asthma-related SAEs with increased daily doses of formoterol, but rather a significant trend in the opposite direction. The authors concluded that, despite reviewing data on over 68,000 patients, the power was insufficient to conclude no increased mortality with formoterol, but that asthma-related SAEs were significantly reduced with formoterol.

A meta-analysis of all studies in which formoterol or salmeterol was used with concomitant ICS was completed by Jaeschke et al.[40]. Based on 62 studies with over 29,000 participants, the authors concluded that in patients with asthma using ICS, LABA use did not increase the risk of asthma-related hospitalizations. The odds-ratio (OR) for all-cause mortality was 1.26 (95% CI: 0.58-2.74) reflecting 14 and 8 deaths in LABA and control groups respectively (Fig. 1). There were 3 asthma-related deaths and 2 asthma-related non-fatal intubations (all in LABA groups, no more than one event per study), too few to establish the effect of LABA on these outcomes. In addition, Bateman et al.[41] reported data from 20,966 participants in 66 studies involving use of ICS with or without salmeterol. Only one death and one intubation were reported, both in patients using salmeterol with ICS, with no difference in hospitalizations. Rodrigo et al.[42] examined asthma exacerbations requiring systemic corticosteroids or hospitalization, life-threatening exacerbations and asthma-related deaths in LABA trials. Asthma related deaths were increased with LABA, but ICS provided a protective effect. LABA with ICS was equivalent to ICS in terms of life-threatening exacerbations and asthma related deaths, and significantly reduced exacerbations (OR: 0.73; 95% CI: 0.67-0.79) and hospitalizations (OR: 0.58; 95% CI: 0.45-0.74).

Salpeter et al.[43] subsequently published quite different results from a further meta-analysis of these existing data, reporting not only that LABA with or without ICS doubled deaths and intubations (OR: 2.10; 95% CI: 1.37-3.22), but also that use of concomitant ICS increased that risk (OR: 3.65; 95% CI: 1.39-9.55)[41]. Even more surprisingly, this meta-analysis reported that LABA used with ICS as an integral part of the study intervention posed an even higher risk of deaths and intubations (OR: 8.19; 95% CI: 1.10-61.18). Critical appraisal of these reported outcomes suggests confounding by ICS dose. In the 12 trials in which asthma-related deaths and intubations occurred, five did not require concomitant ICS (use ranged from 0 to 67%). ICS doses are not provided in three of the remaining seven trials, providing no assurance that equal ICS doses were used in each arm; in one trial ICS plus LABA was compared with higher dose ICS only; and the remaining three studies used two doses of ICS in the LABA and/or non-LABA arms. For a true assessment of safety of LABA, equal doses of ICS are required in each treatment arm with and without LABA to ensure any difference in safety signals reflect the addition of LABA.

A substantive independent meta-analysis involving 110 trials and 60,954 subjects was conducted as part of the FDA evaluation of the safety of LABAs, where the risk differences (RD) for LABA versus non-LABA was calculated[44]. The RD for the composite outcomes of asthma-related death, intubation, or hospitalization for patients receiving LABA without mandatory randomized ICS was significantly

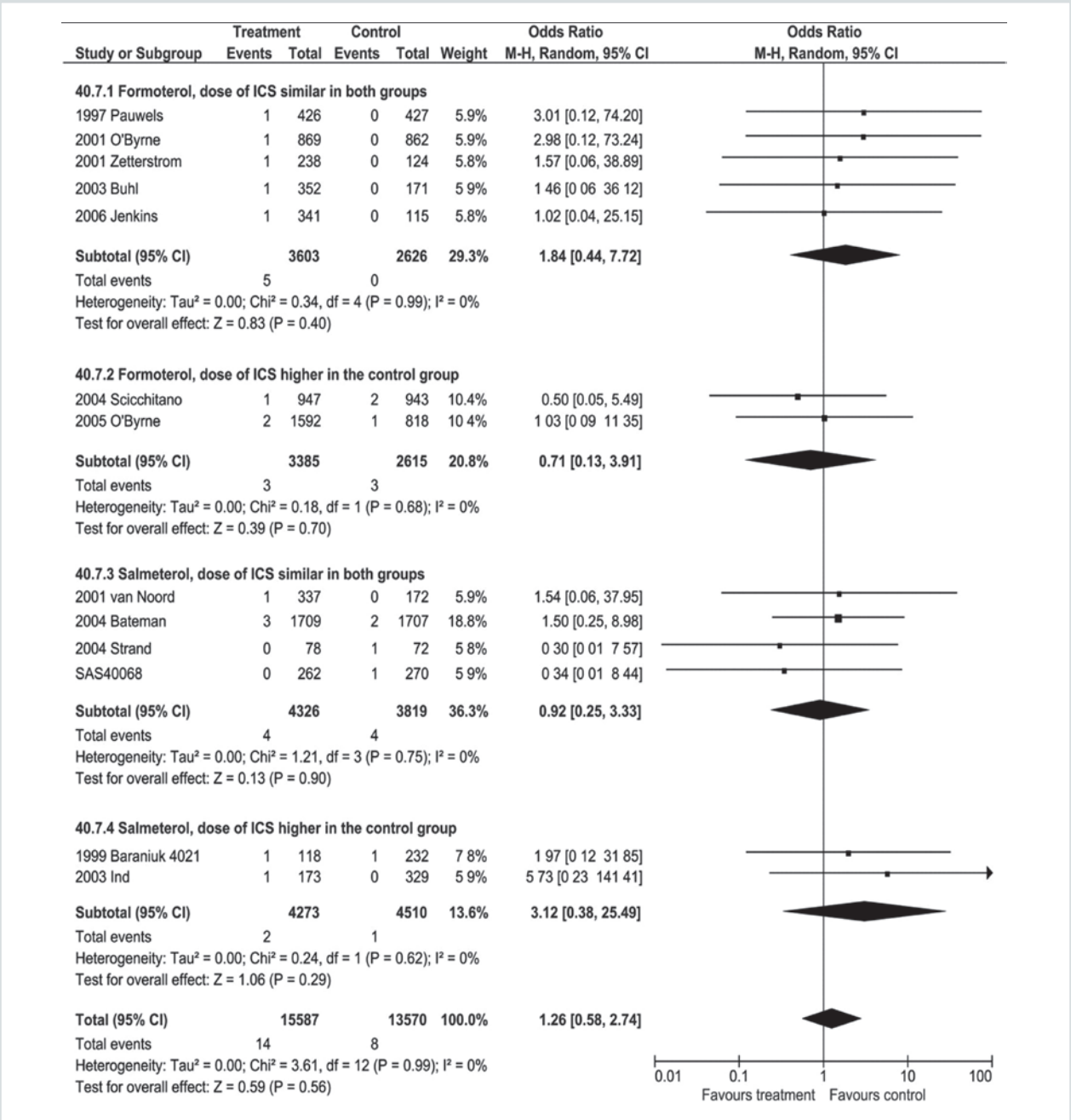

Figure 1. Forest plot of the effects of treatment with long-acting inhaled β_2-agonists (LABA) on total mortality among patients using inhaled corticosteroids (ICS) (only studies with at least one event are presented). No significant increase was demonstrated in patients treated with ICS/LABA combinations *(reproduced with permission from Jaeschke R et al.[40]).*
CI: confidence interval; OR: odds ratio.

increased at 3.63 per 1,000 (95% CI: 1.51- 5.75), whereas among patients receiving LABA with mandatory ICS the RD was not increased at 0.25 per 1,000 (95% CI: –1.69 to 2.18). Furthermore, 43 of 44 deaths and intubations in LABA-exposed patients occurred in trials which

did not mandate the use of ICS, compared with one individual in trials with mandatory ICS. Despite these reassuring data of LABA safety, when used with ICS, a box warning remains on all LABA products in the United States. The FDA has recently provided guidelines suggesting that whenever possible, LABAs should be withdrawn when asthma becomes controlled[45]. However clinical trials have suggested that asthma control worsens following withdrawal of LABA when this has been used to gain control, resulting in a requirement for higher ICS doses[46].

In a response to this divergence in opinion concerning the safety of LABAs when used with an ICS, the FDA required the four pharmaceutical companies marketing LABAs in the United States to each undertake a large randomized controlled study comparing LABA plus ICS with the identical dose of the same ICS, to determine whether there is any safety signal. Four separate studies were conducted in adults; all using essentially the same study design, while one study was conducted in children aged 4-11 years. All studies were multicenter, randomized, double-blind trials with treatment over 6 months. The patient population for each adult study was approximately 11,500 and was 6,500 for the pediatric study, all patients with a history of a severe asthma exacerbation in the previous year. The primary safety endpoint for all of the studies was the first serious asthma-related event (defined as death, endotracheal intubation, or hospitalization). To establish the confidence of non-inferiority in the studies in adults, an upper boundary of the 95% confidence interval for the risk of the primary safety endpoint of less than 2.0 was accepted, while this was less than 2,675 in the pediatric study (which was smaller in size). The efficacy endpoint was time to the first severe asthma exacerbation.

One company withdrew its product (Foradil) from the market very early into the study, which was then discontinued. All of the other studies have been completed and three have been reported in the archival literature. The first adult study to report evaluated the combination of fluticasone-salmeterol to fluticasone alone[47]. The hazard ratio for a serious asthma-related event in the fluticasone-salmeterol group was 1.03 (95% CI: 0.64-1.66), and non-inferiority was achieved. There were no asthma-related deaths in the study; 2 patients in the fluticasone-only group underwent asthma-related intubation (Fig. 2 A). The risk of a severe asthma exacerbation was 21% lower in the fluticasone-salmeterol group. The second adult study compared formoterol-budesonide to budesonide alone[48] (Fig. 3). The hazard ratio for a serious asthma-related event in the budesonide-formoterol group was 1.07 (95% CI: 0.70-1.65) and again non-inferiority was achieved. There were two asthma-related deaths, both in the budesonide-formoterol group; one of these patients had undergone an asthma-related intubation. The risk of an asthma exacerbation was 16.5% lower in the budesonide-formoterol group. The pediatric study also evaluated the combination of fluticasone-salmeterol to fluticasone alone (as this is the only fixed dose combination approved for children in the United States)[49]. The hazard ratio with fluticasone-salmeterol versus fluticasone alone was 1.28 (95% CI: 0.73 to 2.27), which showed the non-inferiority of fluticasone-salmeterol, again with no asthma related deaths (Fig. 2 B). A total 8.5% in the fluticasone-salmeterol group and 10.0% in the fluticasone-alone group had a severe asthma exacerbation. Each of these studies concluded

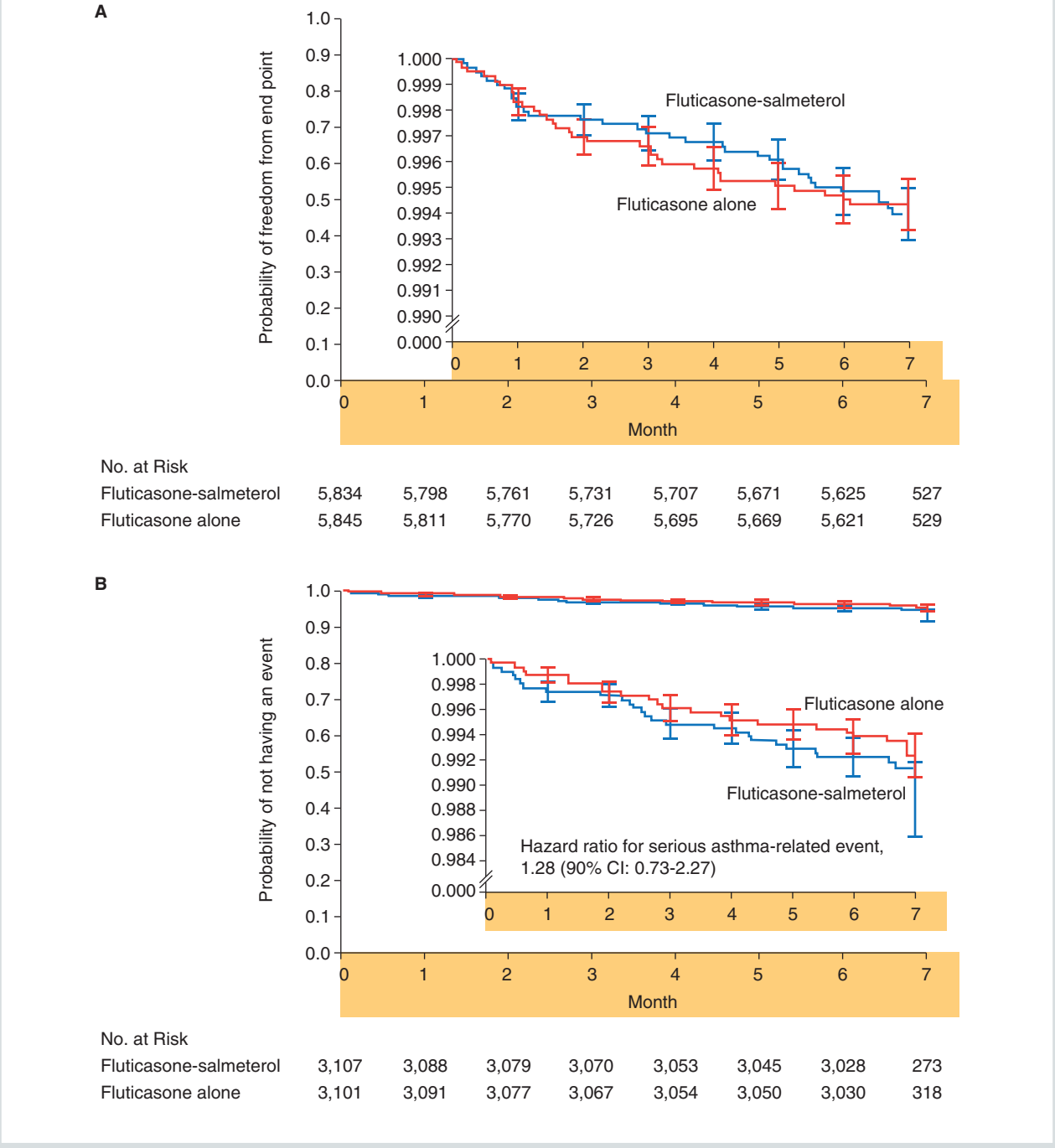

Figure 2. **A:** the first occurance of serious asthma-related events in adult patients, a composite that included death, endotracheal intubation, and hospitalization. Bars indicate standard errors. The hazard ratio for a serious asthma-related event in the fluticasone-salmeterol group was 1.03 (95% CI: 0.64-1.66), and non-inferiority was achieved. The inset shows the same data on an expanded y *axis (reproduced with permission from Stempel DA et al.[47]).* **B:** the first occurrence of serious asthma-related events in the time-to-event analysis in pediatric patients treated with fluticasone/salmeterol or fluticasone alone. The hazard ratio with fluticasone-salmeterol versus fluticasone alone was 1.28 (95% CI: 0.73-2.27), which showed the non-inferiority of fluticasone-salmeterol. The inset shows the same data on an expanded y axis. Bars indicate standard errors *(reproduced with permission from Stempel DA et al.[49]).*

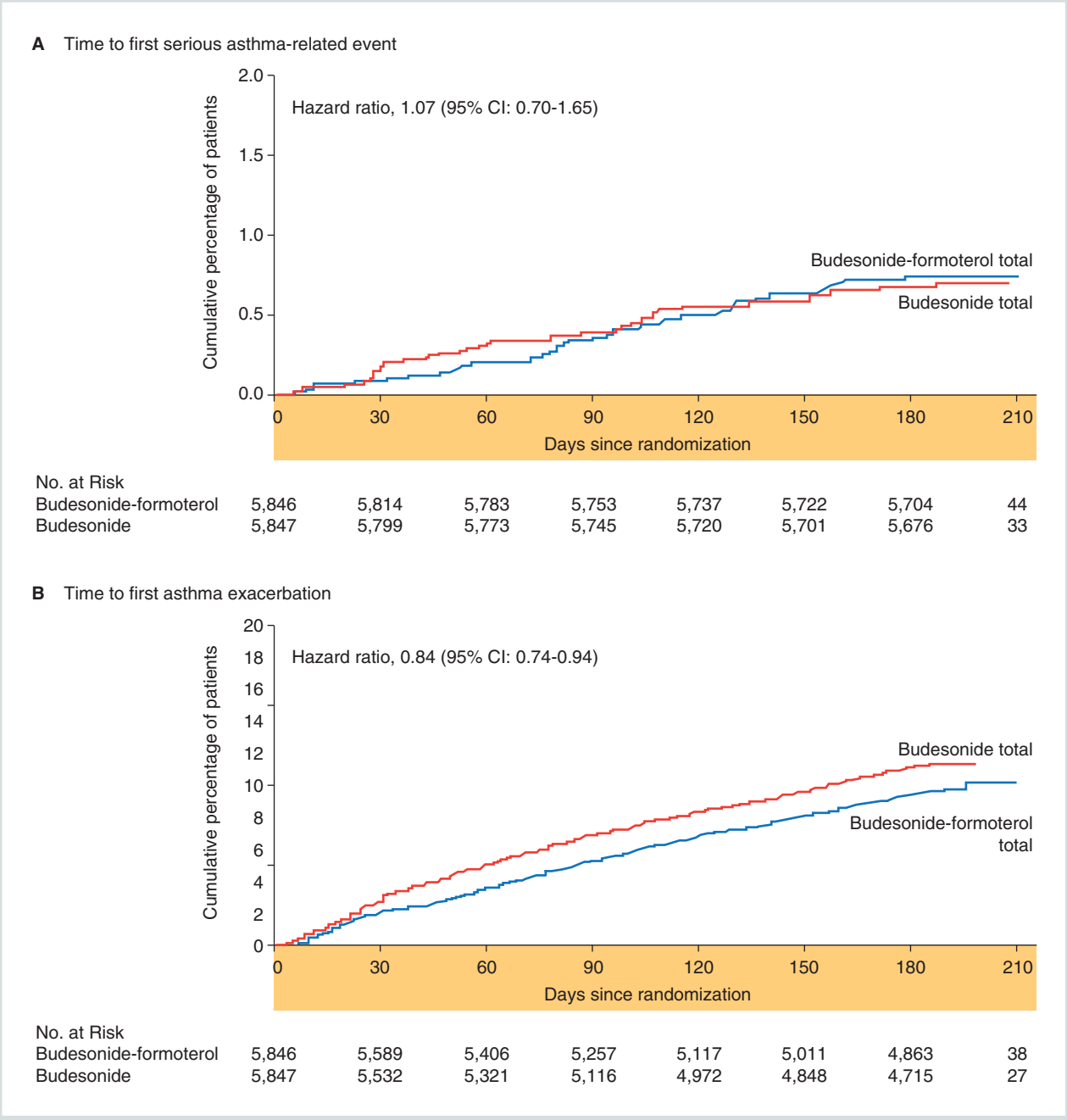

Figure 3. Time-to-event analysis of the risk of a first serious asthma-related event **(A)** and risk of a first asthma exacerbation in patients treated with budesonide/formoterol or budesonide alone in adult patients **(B)**. The hazard ratio for a serious asthma-related event in the budesonide-formoterol group was 1.07 (95% CI: 0.70-1.65) and non-inferiority was achieved, while the risk of an asthma exacerbation was 16.5% lower in the budesonide-formoterol group *(reproduced with permission from Peters SP et al.[48]).*

that patients who received ICS/LABA in a fixed-dose combination did not have a significantly higher risk of serious asthma-related events than did those who received ICS alone, and the fixed-dose combinations reduced the risk of severe asthma exacerbations.

CONCLUSIONS

Inhaled β_2-agonists are a mainstay of asthma treatment. SABAs remain the most widely used asthma medications for relieving symptoms and preventing bronchoconstriction; however, regular use of SABAs as monotherapy in asthma worsens asthma control and their overuse increases the likelihood of asthma-related mortality. LABA monotherapy also increases the risks of asthma-related hospitalization and mortality; however, when used together, particularly in a single inhaler, LABA/ICS combinations improve asthma control, reduce asthma exacerbation risk and allow control to be maintained at a lower overall dose of ICS. Concerns about the risks associated with the use of LABA/ICS combinations have been allayed by the results of several large randomized safety trials conducted both in adults and children.

Given the substantial evidence that patients with asthma use beta-agonists in preference to inhaled corticosteroids when provided in separate inhalers, LABAs should be provided as combination products in a single inhaler in which every dose of LABA is accompanied by ICS.

CONFLICT OF INTEREST

Paul M. O'Byrne reports grants and personal fees from AstraZeneca, personal fees from Chiesi, grants from Novartis, personal fees from Boehringer Ingelheim, personal fees from GSK, grants and personal fees from MedImmune, and personal fees from Merck.

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