

or should not be prescribed for which patients. Perhaps the time has come to acknowledge that the study of genetic variants without concomitant consideration of other determinants of therapeutic efficacy (e.g., specific phenotypic characteristics, race, sex, exposures that trigger symptoms) will provide few results that are useful for our patients. From an ethical point of view, it is imperative for scientists, ethicists, and patient advocates to reach a consensus as to how to apply regulations in a way that will enhance progress in scientific knowledge but also respect and protect the rights of study participants, especially children. This will not be an easy task, given the divergence of opinion among well-intentioned practitioners. Reaching such consensus is, however, mandatory if we expect the public to support and participate in research that is essential for the discovery of new medicines to treat and cure debilitating diseases such as asthma.

Conflict of Interest Statement: F.D.M. received \$5,001 to \$10,000 from MedImmune over 2007–2009, and \$1,001 to \$5,000 from GlaxoSmithKline in 2007 for consultancy activities; he received \$5,001 to \$10,000 from Merck over 2007–2009, and \$1,001 to \$5,000 from MedImmune in 2007 for advisory board activities; and he received \$10,001 to \$50,000 in 2007–2009 from Merck in lecture fees. L.M.F. received \$10,001 to \$50,000 in consultancy fees from Nycomed, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Roche, and Pfizer; he has received \$10,001 to \$50,000 from Nycomed in advisory board fees; he has received \$1,001 to \$5,000 in lecture fees from Nycomed, AstraZeneca, Abbott, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, UCB, Roche, and Pfizer; and he has received sponsored grants for \$10,001 to \$50,000 from Nycomed, Abbott, AstraZeneca, Boehringer Ingelheim, Menarini, Schering Plough, Chiesi Farmaceutici, Novartis, GlaxoSmithKline, Merck Sharp & Dohme, UCB, and Pfizer.

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Meeting the Obligation to Balance Bioethics and Clinical Trial Design in Asthma

The above editorial by Dr. Martinez and Dr. Fabbri in this issue of the *Journal* (pp. 647–648 [1]) commenting on our article (pp. 676–687 [2]) raises complex issues relevant to the use of long-acting bronchodilators (LABA) in the treatment of asthma and states that “acquiring knowledge about the use of LABA alone would have no practical application.” We respectfully disagree with this statement.

Previous studies have suggested that ADRB2 Arg16Gly polymorphisms may alter clinical responses to short- and long-acting β -agonists (SABA, LABA). Several studies supporting this finding were conducted with SABAs in the absence of inhaled

corticosteroids (ICS) (2, 3), or when ICS were permitted but not required (5–7).

Results of pharmacogenetic studies assessing LABA responses based on Arg16Gly polymorphisms have been mixed since initial small retrospective studies using salmeterol suggested that clinical responses may be affected by Arg16Gly polymorphisms with or without concomitant ICS (8), whereas larger retrospective studies with salmeterol or formoterol found no pharmacogenetic associations in the presence of ICS (5, 9, 10). The editorial by Taylor and Hall in the *Lancet*, which accompanied the latter study, pointed out that it was unknown

whether ICS may be “protective” from potential deleterious effects of LABA (11). Therefore, a study design using LABA without ICS was needed to determine if there were intrinsic pharmacogenetic effects in individuals with possible risk genotypes. The alternative study arm of salmeterol with concurrent ICS investigated whether protection was produced by concomitant ICS. The study results reported in this paper showed that Arg16Gly polymorphisms did not alter the clinical responses to salmeterol in the presence or absence of ICS.

It is recognized that therapy with LABA alone is not recommended, however, for the treatment of patients with persistent asthma. It is also recognized that salmeterol and ICS are available as separate inhalers for some patients with asthma, and that selective discontinuation of the ICS component, or use of salmeterol alone, can occur in the community. This genotype-stratified trial design comparing salmeterol and concurrent ICS with salmeterol alone was presented as part of a more comprehensive study plan to evaluate potential adverse effects of β_2 -adrenergic therapy at the 2005 U.S. Food and Drug Administration Advisory Committee meeting on LABA safety. In addition, during the most recent U.S. Food and Drug Administration Advisory Committee meeting on LABA safety in December 2008, studies in at-risk populations and pediatric populations were requested.

To study LABA therapy alone, the current study design carefully considered the specific target population and only enrolled patients who were not treated with concurrent ICS (those who were controlled on SABA only). To ensure reasonable control of asthma at the time of screening, patients could have no history of life-threatening asthma, have no hospitalization for asthma within the last 6 months, and have a mean FEV₁ of 82% predicted at baseline. Each patient had to complete two separate 8-week run-in periods, first on as-needed SABA alone, and then on as-needed ipratropium alone. In addition, each patient was seen in the clinic every 28 days and was instructed to follow an action plan that specified prompt evaluation by the clinical centers should their asthma worsen. This included instruction to call the investigator if their peak flow, which was monitored daily, showed deterioration or fell below a predefined stability limit, even if the patient was not experiencing symptoms. One subject who developed worsening asthma did not follow the action plan and self-treated with oral prednisone. Unfortunately, after 4 days, the subject went to an acute care center and died after aspirating during transfer to a larger facility. Each subject provided written informed consent. The purpose of the study, the procedures used, the expected benefits to the participant and/or society, the potential of reasonably foreseeable risks, and alternatives to participating in the study were fully described. In addition, the consent included specific information describing the results of the Salmeterol Multicenter Asthma Research Trial (12). Each subject had the opportunity to ask questions and have them answered by one of the investigators. For adolescent minor subjects, the parent or legal guardian provided consent with the understanding that consent to participate in the study must be voluntary for both the guardian and the participant and free of any coercion or promises of benefit. As required by Federal Regulations (21 CFR Part 56), the consent and study was approved by an institutional review board (IRB) for each study site. Under these regulations, each IRB also has the responsibility to ensure that “(I) risks to subjects are minimized: By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk... (2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distin-

guished from the risks and benefits that subjects would receive even if not participating in the research)... (3) Selection of subjects is equitable...” Because more than 16 different IRBs reviewed the protocol and consent, and approved the study, there was evidence for adequate equipoise of safety consideration and efficacy between study arms.

The editorial comments from Drs. Martinez and Fabbri suggested that salmeterol caused an increase in exacerbations (1). At study entry, subjects were not treated with ICS and controlled their asthma with SABA only. The number of exacerbations during the two 8-week run-in periods while receiving short-acting bronchodilators (albuterol or ipratropium) alone, was 35, compared with 10 during the 16-week treatment period with salmeterol and only 1 during combination ICS therapy. Accounting for differences in relative exposure, the occurrence of exacerbations in patients receiving salmeterol actually was lower than the occurrence of exacerbations in patients receiving short-acting bronchodilators only. Interestingly, during the as-needed albuterol and ipratropium open label run-in period there were more exacerbations in Arg/Arg homozygotes than in other Arg16Gly genotypes ($P < 0.025$), suggesting that Arg/Arg homozygotes may represent an exacerbation risk genotype regardless of treatment.

We agree with Drs. Martinez and Fabbri that it is “imperative for scientists, ethicists, and patient advocates to reach consensus on how to apply regulations in a way that will enhance progress in scientific knowledge” (1). Current guidelines and medical governance practices are designed to protect the welfare of subjects and represent the underlying principles followed in the development and design of the current study. Furthermore, scientists and investigators must remain vigilant in protecting patient welfare within the balance of studies designed to provide scientific information relevant to the discovery of new medications and to further inform on the appropriate use of medicines approved within the community. Although ethical considerations are paramount in the design and execution of clinical trials, there remains the requirement to conduct appropriate evidence-based studies to understand potential risks (e.g., pharmacogenetic) associated with medications to guide clinical care and provide information that forms a scientific basis for management guidelines.

Conflict of Interest Statement: E.R.B. has received consultancy fees (\$5,001–\$10,000), advisory board fees (\$5,001–\$10,000), and lecture fees (\$5,001–\$10,000) from GlaxoSmithKline over the last 3 years, and industry-sponsored grants from GlaxoSmithKline (\$5,001–\$10,000). H.S.N. has received consultancy fees from AstraZeneca (\$10,001–\$50,000) over the last 3 years and advisory board fees over the last 3 years from Schering Plough (\$5,001–\$10,000), GlaxoSmithKline (\$5,001–\$10,000), Genentech/Novartis (\$1,001–\$5,000), and Abbott (\$1,001–\$5,000). He has received lecture fees from GlaxoSmithKline (\$50,001–\$100,000 over the last 3 years) and institutional industry-sponsored grants from GlaxoSmithKline (more than \$100,000), AstraZeneca (more than \$100,000), Schering Plough (more than \$100,000), Ception (\$50,001–\$100,000), and Genentech/Novartis (more than \$100,000). M.K. has received advisory board fees from GlaxoSmithKline, Sepracor, and Merck (all for \$1,001–\$5,000); she has received lecture fees from Merck and GlaxoSmithKline (both for \$5,001–\$10,000); she has received industry-sponsored grants from GlaxoSmithKline (more than \$100,000), Asthmatx (\$50,001–\$100,000), Bio-Marck (\$10,001–\$50,000), Broncus (\$10,001–\$50,000), and GE Healthcare (more than \$100,000); she has received \$1,001–\$5,000 from Genentech for an EXCELS clinical trial and more than \$100,000 from Novartis for an IL-13 Phase II trial; and she has received sponsored grants from NIH (more than \$100,000), American Lung Association (\$50,001–\$100,000), and Parker B. Francis (\$50,001–\$100,000). J.C. has received consultancy fees from Amgen (up to \$1,000); lecture fees from SP (\$1,001–\$5,000), Merck (\$1,001–\$5,000), and GlaxoSmithKline (\$5,001–\$10,000); expert witness fees (\$5,001–\$10,000) related to mold litigation; and industry-sponsored grants from Amgen (\$50,001–\$100,000), MedImmune (\$50,001–\$100,000), Genentech (\$50,001–\$100,000), and Novartis (\$10,001–\$50,000). D.A.M. has acted as a consultant for GlaxoSmithKline for no compensation. S.W.Y. is a full-time employee of GlaxoSmithKline; he holds stock from GlaxoSmithKline, which he has been granted as a full-time employee. W.H.A. is a full-time employee of GlaxoSmithKline; he holds stock from GlaxoSmithKline, which he has been granted as a full-time

employee; he has received a patent from GlaxoSmithKline related to PC_x of markers of leukotriene modulators response in asthma (unrelated to the subject matter of this manuscript); GlaxoSmithKline has been a supporter of programs that have provided support for ATS activities. A.H.E. is a full-time employee of GlaxoSmithKline; she holds \$1,001–\$5,000 of GlaxoSmithKline stock. H.G.O. is a full-time employee of GlaxoSmithKline; he owns \$10,001–\$50,000 in GlaxoSmithKline stock.

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Control of Hypertension in Nonsleepy Patients with Obstructive Sleep Apnea

In this issue of the *Journal* (pp. 718–726), Barbé and colleagues describe the results of a multicenter study aimed at exploring the long-term effects of continuous positive air pressure (CPAP) ventilation on hypertension control in patients with obstructive sleep apnea (OSA) (1). The demonstration of a close link between OSA and hypertension has been provided by longitudinal investigations supporting the hypothesis of a causal link between OSA and the appearance or worsening of a high blood pressure condition (2, 3). Based on such data, the presence and severity of repeated airway obstruction during sleep may represent an independent risk factor for a persistent increase in blood pressure values often associated with a loss of the typical “dipping” pattern during ambulatory blood pressure monitoring (4, 5).

The mechanisms responsible for hypertension in OSA are only partly understood. Alterations in autonomic responses, with increased sympathetic activity secondary to chemoreflex stimulation by repeated hypoxemia, have been reported to play an important role, together with disruption of ventilatory mechanics, activation of inflammatory processes, endothelial dysfunction, and alterations in arousal mechanisms (2, 6, 7). In

particular, the occurrence of autonomic dysfunction in OSA has been demonstrated through assessment of plasma and urinary catecholamines as well as microneurographic recordings from peroneal nerves. Alterations in autonomic cardiovascular modulation in OSA have also been shown through time and frequency domain computer analysis of continuous blood pressure and heart rate tracings, obtained either during wakefulness or sleep (8–10). Alterations in cardiac autonomic function, as quantified by heart rate variability and spontaneous baroreflex sensitivity analysis, seem to be particularly pronounced in patients with OSA affected by daytime somnolence (11), suggesting that daytime sleepiness may represent an additional factor increasing the likelihood of developing hypertension in patients with OSA.

OSA-related hypertension is often difficult to control pharmacologically (12). Indeed, recent hypertension management guidelines (e.g., JNC VII and ESH-ESC 2007 recommendations) highlight OSA as an important identifiable cause of resistant hypertension (13, 14). Although anti-hypertensive treatment may not easily control hypertension in patients with OSA, treatment