Inhaled β-agonists significantly prolong the QTc interval in a dose-dependent and gene-dependent manner. While the prolongation of QTc is a risk for torsades de pointes, a necessary cofactor appears to be increased transmural dispersion of repolarization. Transmural dispersion of repolarization is sympathetically mediated and has been demonstrated to increase with therapy with systemic β-agonists, but is likely affected by inhaled agents as well.

The race aspects of the findings in the SMART are particularly interesting because the risk of drug-induced torsades de pointes with β-agonist therapy is dependent on genetic polymorphisms for the genes associated with the long QT syndrome. It has been shown that African Americans have substantially greater heterogeneity in those genes, a finding of as yet still unknown consequence. While we are in the process of conducting a trial comparing the effects of albuterol on QTc in asthmatic patients compared to nonasthmatic patients, it would be helpful to know specifically what the cause of death was in the SMART trial in the 11 patients who died while receiving salmeterol, but whose causes of death were not ruled to be asthma and thus were not detailed in the study.

Additionally, of the 13 reported deaths in the salmeterol group that were ruled to be asthma-related, 7 listed either no cause of death or a primary cardiovascular disorder on the death certificate (Table 5 in the article by Nelson et al1). While I noted that a coroners report was available for one patient, it would be helpful to know whether further autopsy data are available or are being sought since previous series have reported autopsy findings that are inconsistent with a pulmonary cause of death in patients who have been reported to have died of asthma.

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To The Editor:

We find Dr. William’s letter quite interesting, particularly as it relates to polymorphisms within genes associated with the long-QT syndrome and the heterogeneity of these genes in African Americans. The protocol for Salmeterol Multicenter Asthma Research Trial (SMART) did not specify the collection of biological material for genotyping, which we acknowledge could have helped to clarify some of the observations seen in the African-American population. We do not have any more detailed information for the subjects in the salmeterol group who either had no listed cause of death or a primary cardiovascular cause, as the published information is all that is available.

Although β-agonists can produce ECG changes, prolongation of the QTc interval, and ST-segment depression, previous studies addressing the cardiovascular effects of salmeterol when taken at the recommended doses have not demonstrated an increase in QTc intervals or an increased incidence of supraventricular or ventricular ectopy. On the other hand, there is the possibility that some subjects in SMART could have taken doses of salmeterol that were higher than the recommended dose. Salmeterol, like all β-agonists, may produce dose-related increases in cardiac electrophysiologic abnormalities. Even so, the numbers of serious adverse events in the cardiovascular system were similar for subjects in both treatment arms in SMART and occurred at a rate of < 1%.

Dr. Nelson is a consultant, speaker, and recipient of research grants from GlaxoSmithKline, and was also a member of the Morbidity and Mortality Review Committee. Dr. Dorinsky is an employee of GlaxoSmithKline.

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Comments on the Salmeterol Multicenter Asthma Research Trial

To the Editor:

The Salmeterol Multicenter Asthma Research Trial (SMART) was initiated to further explore the signal for asthma-related death seen in the Serevent Nationwide Surveillance Study in light of US postmarketing reports of asthma fatalities associated with salmeterol. SMART confirms the earlier findings that salmeterol use leads to an increased incidence of asthma-related death. We have two comments on the report by Nelson et al.

The authors note that certain end points in SMART did not reach statistical significance. While true, in interpreting the meaning of this failure to reach statistical significance, the premature termina-
tion of the study has to be considered. For example, while there was no statistically significant difference between treatment groups for the primary end point (respiratory-related death or life-threatening experience: risk ratio, 1.40; 95% confidence interval, 0.9 to 2.1), if the study had continued as planned, it is likely that this comparison would have reached statistical significance.

It is also unclear why certain analyses were included in the report; for instance, data are included from the 28-week treatment period combined with data spontaneously reported for a 6-month poststudy period (Table 6). The authors state that patients may have continued to take unused study medication after the study was completed. However, it is possible that placebo-treated patients could have initiated treatment with salmeterol following their participation in the study, which would obscure any treatment effect. Also, the authors included analyses based on an artificial division of the study into two “phases,” based on different recruitment strategies. Whether this post hoc, exploratory analysis was initiated based on a scientific hypothesis or data dredging is unclear. Nonetheless, in both phases, there were more asthma-related deaths in the salmeterol group. Interested readers may review the proceedings of the Food and Drug Administration advisory committee convened to discuss SMART and the public statements issued by the Food and Drug Administration.

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REFERENCES


To the Editor:

The data collection and analysis of the Salmeterol Multicenter Asthma Research Trial were conducted with rigor, scientific integrity, and without known bias; our article was a transparent, peer-reviewed communication designed to inform health-care practitioners.

Dr. Seymour questions why data from the 28-week treatment period plus a 6-month follow-up period were included along with data from the 28-week treatment period. The protocol included a 6-month follow-up because patients received 6 months of therapy and underwent minimal procedures to retrieve unused medication. It is well-recognized that medication therapy compliance is poor; therefore, patients may have had study medication left and continued to take it beyond the 28-week period. Although it is possible that patients receiving placebo may have initiated salmeterol therapy after the study, the only planned analysis included the data from the 28-week treatment period plus the additional 6-month follow-up period, which were provided to an independent Data Safety Monitoring Board and subsequently to the US Food and Drug Administration (FDA). After study termination and the reporting on the interim analysis, further discussions with the US FDA led to an agreement to focus the analysis on the 28-week treatment period, although no substantial differences exist between the analysis of the 28-week treatment period and that of the 28-week treatment period plus the 6-month follow-up period.

Dr. Seymour further questions the data reported for the two distinct phases. These data were acknowledged in the article as being exploratory. It is well-recognized that study design and recruitment approaches can lead to confounding in studies. Switching from media-driven recruitment, yielding 13 asthma-related deaths in 15,342 patients (phase I), to investigator-driven recruitment, yielding 3 asthma-related deaths in 11,013 patients (phase II), suggests that the recruitment approach may have affected outcomes. Furthermore, the quality of care and the physician-patient relationship can affect outcomes and were likely different between the phases, providing the scientific basis for this analysis.

We agree that interested readers should review the breadth of the data and the proceedings of the US FDA advisory committee that was convened to discuss long-acting β-agonists.

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Disposable vs Reusable Bronchoscope Valves

To the Editor:

Mehta et al should be congratulated for developing a much-needed American College of Chest Physicians/American Association for Bronchology (ACCP/AAB) consensus statement on preventing infections associated with flexible bronchoscopy, which recently appeared in CHEST (September 2005). However, at issue are specific ACCP/AAB recommendations to use only bronchoscopes that have “disposable suction valves and biopsy valves” and that “nonimmersible bronchoscopes and those with a reusable valve should be replaced as soon as possible.”

These well-intentioned recommendations essentially contraindicate the use of many existing scope/valve designs, and end users may feel compelled to discard their current equipment utilizing reusable valves and seek replacement instruments utilizing only