The Salmeterol Multicenter Asthma Research Trial

To the Editor:

Nelson et al. discuss an apparent lower rate of deaths associated with salmeterol in the Salmeterol Multicenter Asthma Research Trial (SMART) [1.22 per 1,000 person-years] compared with the previous UK surveillance study [2.32 per 1,000 person-years]. However, this low rate cannot be verified from their data. There were 13 deaths in 13,176 salmeterol-treated patients, with median treatment duration of 197 days. Hence, the death rate is (13/13.176) × (365/197), namely 1.83 deaths per 1,000 person-years. Given 22% discontinued prematurely, mean rather than median treatment duration should be the denominator, and so even 1.83 deaths per 1,000 person-years is an underestimate of the true risk.

It is unclear how Nelson et al. calculated the risk of 1.22 per 1,000 person-years (see page 25 of their report). Does this rate refer to white patients only? Six deaths among 9,281 white patients gives (6/9.281) × (365/197) or 1.20 deaths per 1,000 person-years. If so, the calculation for African-American patients should also be reported, namely (7/2.366) × (365/197) or 5.48 deaths per 1,000 person-years.

Ages at death in the salmeterol-treated patients were 14, 37, 41, 46, 47, 47, 51, 56, 60, 62, and 67 years, similar to those deaths in the UK study. The true comparators for these study populations are death rates for their age group, not for the total population, as most asthma deaths occur in the elderly. In the United States from 1990 to 2001, mortality from asthma as the underlying cause of death in the population aged 45 to 64 years (the majority of those dying in the SMART) was 2.4 per 100,000. Using a conservative 5% prevalence for adult asthma, this translates to a rate of 0.48 per 1,000 person-years. Hence, the death rate in the SMART is approximately fourfold higher than would be expected in the US asthmatic population of that age.

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To the Editor:

We appreciate Dr. Sears’ comment regarding the asthma-related death rate for salmeterol recipients in the Salmeterol Multicenter Asthma Research Trial (SMART). In the “Discussion” section, we inadvertently listed the asthma death rate for the total population (1.22 per 1,000 person-years). The asthma death rate for subjects exposed to salmeterol in SMART was 1.98 per 1,000 person-years. However, the conclusions regarding the asthma death rate with regard to Castle et al. and Martin and Shakir remain unchanged. We have submitted a correction to the journal with this information.

As the number of asthma-related deaths in SMART for subjects receiving salmeterol was extremely low (approximately 10 deaths in 10,000 subjects), extrapolation of the death rate to larger populations, such as the US population of subjects with asthma, should be interpreted with caution. In addition, applying rates obtained from subpopulations, such as certain age groups, can further decrease the accuracy of the results due to an even smaller number of events, and without appropriate context such extrapolations can be misleading.

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928
in asthmatic patients who require regular bronchodilator treatment. BMJ 1993; 306:1034–1037

Why SMART About Second-Line Treatment When First-Line Treatment Is Being Ignored?

To the Editor:

In a recent issue of CHEST (January 2006),¹ the Salmeterol Multicenter Asthma Research Trial (or SMART) demonstrated that the regular use of a twice-daily regimen of salmeterol in asthmatic patients was associated with an unmerging increase in respiratory-related and asthma-related deaths, combined asthma-related deaths, or life-threatening experiences. However, surely one of the other most concerning observations was the fact that at study entry only 47% individuals in both the active treatment and placebo groups were receiving regular therapy with inhaled corticosteroids. Thus, > 26,000 subjects with asthma of approximately 16 years duration with a mean peak expiratory flow of 84% predicted were randomized to receive either a placebo inhaler or a long-acting β₂-agonist over a 28-week period without therapy with inhaled corticosteroids.

Since guidelines²,³ advocate the early use of inhaled corticosteroids in the treatment of asthma, it is therefore incredulous to consider that the investigators felt it reasonable to enroll a majority of individuals who were being inappropriately managed. In the community. Perhaps rigorous advertising campaigns are required to emphasize that therapy with inhaled corticosteroids is a long-established, effective, safe, and inexpensive treatment for the management of asthma. And perhaps clinicians and the pharmaceutical industry require reminding too.

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Dr. Currie has received funding from GlaxoSmithKline for attending postgraduate educational meetings and honoraria for giving talks.

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Cause of Death in the SMART Trial

To the Editor:

The Salmeterol Multicenter Asthma Research Trial (SMART)¹ found a higher incidence of death in African Americans with salmeterol therapy compared to placebo. The authors speculated on possible genetic causes, mentioning β-receptor polymorphisms. But another genetic aspect is worth considering.

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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 al.). While I noted that a coroner's 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 β2-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%.

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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 postmarket 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-
sion 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 authors3 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.4

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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).1 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.”1

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
disposable valves. Pentax Medical Company believes these specific recommendations are unnecessary, financially imprudent, and without scientific basis or documented evidence.

In compliance with current regulations and guidance for reusable medical devices,2,3 manufacturers should provide microbiologically validated reprocessing instructions for cleaning and high-level disinfection (or sterilization) of the endoscope and reusable endoscope components (valves). Provided that manufacturer-validated instructions are supported by simulated-use studies and end users strictly adhere to these recommendations, reusable scope components (valves) should be an acceptable alternative to disposable components for semicritical devices, including bronchoscopes.

The reference4 to support the ACCP/AAB recommendation described a 1986 incident identifying one brand/design and involved a questionably inferior valve design unlike the valves of other manufacturers. Many years of experience has demonstrated that reusable valves, if reprocessed in strict accordance with the validated recommendations of the manufacturer, have not been reported to be vectors of infection. While we recognize the potential for possible contamination of valves, we believe the same potential risks exist whenever any endoscope instrument and/or scope component is not reprocessed in strict accordance with the validated instructions of the manufacturer. We hope that the ACCP/AAB can reconsider its current position and accept the use of reusable valves reprocessed by validated high-level disinfection or sterilization processes.

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To the Editor:

We thank Mr. Nelson for his interest in the consensus statement on the prevention of flexible bronchoscopy-associated infections (November 2005).1 We also appreciate Mr. Nelson’s concerns regarding the recommendation to replace flexible bronchoscopes equipped with reusable biopsy valves with flexible bronchoscopes equipped with the disposable valves.

A faulty valve design was deemed responsible for the outbreaks of “true” as well as “pseudo” infections related to flexible bronchoscope in a significant number of patients.5,6 These events prompted the development of the consensus. We recognize that several flexible bronchoscope manufacturers have introduced a number of flexible bronchoscope models, and that each of these models has suction and biopsy ports capped with valves of different designs. Therefore, it was beyond the scope of the consensus statement to review each of these valve designs and make specific comments. It was the decision of the committee to make the safest recommendation for using disposable valves. We agree with Mr. Nelson that if a manufacturer of the flexible bronchoscope can ensure the proper sterilization of a reusable valve each time, that should be acceptable.

The consensus statement “highly recommends” and does not mandate the practice or set a time limit. We believe that the financial burden of replacing expensive flexible bronchoscopes would strongly encourage strict adherence to the disinfection practices or the use of properly sterilized reusable valves. We once again stress that, due to the lack of adequate scientific evidence, this consensus statement was based on the opinions of experts.

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