

Hospitalizations and Mortality in the Lung Health Study

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This report deals with deaths and hospitalizations during the 5-year Lung Health Study, as documented by examination of appropriate records. There were 149 deaths (2.5%) during the study, caused largely by lung cancer and cardiovascular disease, particularly coronary heart disease. A total of 12.8% of participants were hospitalized, with cancer, cardiovascular disease, and nonmalignant respiratory disease accounting for 75% of hospitalizations. There were no significant differences among the original treatment groups for all-cause mortality, lung cancer, or hospitalizations for respiratory disease. Deaths and hospitalizations for cardiovascular disease and coronary artery disease were more common in the smoking intervention plus Atrovent inhaler (SI-A) group, which received ipratropium bromide, than in the smoking intervention plus placebo inhaler (SI-P) group, which received placebo, and the differences approached statistical significance. However, we were unable to find a dose effect, in that differences were not related to self-reported inhaler compliance. In the SI-A group, nine participants were hospitalized for supraventricular tachycardia as compared with two in the SI-P group, and SI-A participants with this condition were unusually compliant with their inhaled medication. When all participants were considered and smoking status considered as a time-dependent covariate, smoking cessation was associated with significant reductions in fatal or nonfatal cardiovascular disease and coronary artery disease.

Keywords: chronic obstructive pulmonary disease; anticholinergic; smoking; mortality; morbidity

The Lung Health Study (LHS) was a cooperative 10-center randomized clinical trial involving 5,887 smokers, aged 35 to 60, who did not regard themselves as ill but who had mild to moderate lung function impairment. Individuals with serious disease, excessive alcohol intake, hypertension, or obesity were excluded. The overall objective was to determine whether a program incorporating intensive smoking intervention and prescription of an inhaled bronchodilator could prevent or delay the onset of clinically apparent chronic obstructive pulmonary disease. The specific primary endpoints of the study were defined in advance as (1) the rate of decline in 1-second forced expiratory volume over a 5-year follow-up period, and (2) the incidence of respiratory and cardiovascular morbidity and mortality over the same period.

The effects of intervention and smoking cessation on 5-year rates of decline of 1-second forced expiratory volume have been reported (1, 2). A positive and cumulative effect of smoking intervention was demonstrated. The effects were

largest in participants who quit smoking early in the study and did not relapse. The bronchodilator (ipratropium bromide, Atrovent, supplied to the study by Boehringer-Ingelheim Pharmaceuticals, Inc., Ridgefield, CT) produced a relatively small and noncumulative improvement in 1-second forced expiratory volume, which reversed when the drug was withdrawn (1).

The purpose of this article is to present the effects of smoking intervention and the use of the inhaled bronchodilator on mortality and morbidity over the 5 years after randomization into the study.

METHODS

The design of the LHS has been described in detail (3). Participants were randomized to three groups: (1) smoking intervention plus Atrovent inhalers (SI-A), (2) smoking intervention plus placebo inhalers (SI-P), and (3) usual care (UC). Participants had annual clinic visits for 5 years that included questionnaires on smoking, use of prescription drugs, serious illnesses, hospitalizations, and physician visits.

Participants in the two SI groups were offered an intensive 10-week smoking intervention program and either inhaled ipratropium (SI-A) or placebo (SI-P). They were scheduled for visits at 4-month intervals to encourage compliance. Self-reported smoking status was validated biochemically. Inhaler compliance was ascertained from self-report. They were instructed to take two puffs from their inhalers three times a day.

If a participant had been hospitalized, copies of essential documents were obtained from hospital record rooms. Records that made significant mention of respiratory or cardiovascular disease (CVD) or cancer were forwarded to the study's mortality and morbidity review board for definitive coding. The mortality and morbidity review board was also responsible for classifying the causes of death for all participants who died during the study. They reviewed death certificates, autopsy reports, relevant hospital records, and summaries of interviews with attending physicians, or eyewitnesses.

Participants were categorized as sustained quitters if they were biochemically validated nonsmokers at each annual visit. Participants who were smokers at each annual visit were continuing smokers. Those whose behavior varied were classified as intermittent quitters.

Participants who reported using three or more puffs per day from their inhalers were classified as "satisfactory" users. Participants whose compliance was satisfactory at all annual visits were categorized as sustained satisfactory compliers. Those with unsatisfactory compliance at all annual visits were categorized as continuing unsatisfactory. Participants whose behavior varied were categorized as intermittently satisfactory. In addition, compliance at 4-month visits was coded on a 0- to 4-point scale: 0, zero puffs; 1, less than one puff; 2, at least one but less than three puffs; 3, at least three but less than four puffs; and 4, four or more puffs. Mortality endpoints were as follows: (1) death from any cause, (2) death from coronary heart disease (CHD), (3) death from CVD, including all CHD deaths, and (4) death from lung cancer. Nonfatal hospitalizations were analyzed if they were considered to be caused by (1) CHD, (2) CVD, including all CHD, (3) lung cancer, and (4) nonmalignant diseases of the lower respiratory tract.

Differences between groups were tested using analysis of variance, chi-square statistics, and Fisher's exact test. Times to events were analyzed using the Kaplan-Meier product-limit method (4). Differences among the three treatment groups were analyzed with omnibus tests; differences between pairs of groups were not adjusted for multi-

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TABLE 1. SELECTED BASELINE CHARACTERISTICS AND FOLLOW-UP RATES OF LUNG HEALTH STUDY PARTICIPANTS AT ANNUAL VISITS BY TREATMENT GROUP*

| Baseline Variable | SI-A (n = 1,961) | | SI-P (n = 1,962) | | UC (n = 1,964) | |
|---|------------------|------|------------------|------|----------------|------|
| | Mean | SD | Mean | SD | Mean | SD |
| Age, yrs | 48.4 | 6.8 | 48.6 | 6.8 | 48.4 | 6.8 |
| Male, % [†] | 60.8 | 48.8 | 64.0 | 48.0 | 63.8 | 48.1 |
| Cigarettes per day | 31.2 | 13.2 | 31.5 | 12.6 | 31.1 | 12.8 |
| Pack-years | 40.4 | 19.7 | 40.4 | 18.8 | 40.5 | 18.9 |
| Body mass index, kg/m ² | 25.5 | 3.9 | 25.7 | 3.9 | 25.6 | 3.9 |
| Systolic BP, mm Hg | 120.3 | 13.9 | 120.5 | 14.1 | 120.6 | 13.8 |
| Diastolic BP, mm Hg | 76.9 | 9.3 | 77.2 | 9.4 | 77.2 | 9.3 |
| Married, % [‡] | 71.1 | 45.3 | 72.9 | 44.5 | 69.5 | 46.1 |
| Education, yrs | 13.6 | 2.8 | 13.6 | 2.8 | 13.7 | 2.8 |
| Nonwhite race, % | 4.1 | 19.8 | 4.2 | 20.1 | 4.4 | 20.5 |
| Drink alcohol, % | 70.0 | 45.8 | 70.6 | 45.6 | 70.1 | 45.8 |
| Drinks per week in those who drink alcohol | 6.1 | 5.8 | 6.2 | 5.7 | 6.2 | 5.6 |
| FEV ₁ % predicted | 74.8 | 9.5 | 75.1 | 9.5 | 74.8 | 9.5 |
| FVC % predicted | 96.3 | 11.1 | 96.3 | 10.7 | 96.3 | 10.8 |
| FEV ₁ /FVC, % | 63.0 | 6.0 | 63.2 | 6.0 | 62.9 | 6.0 |
| Contact and forms completion rates at annual visits | | | | | | |
| Year 1 | | 96% | | 95% | | 95% |
| Year 2 | | 95% | | 94% | | 95% |
| Year 3 | | 94% | | 94% | | 94% |
| Year 4 | | 94% | | 93% | | 93% |
| Year 5 | | 97% | | 97% | | 96% |

Definition of abbreviations: BP = blood pressure; FEV₁ = forced expiratory volume at 1 second; SI-A = smoking intervention plus Atrovent; SI-P = smoking intervention plus placebo; UC = usual care.

* The treatment groups did not differ significantly ($\alpha = 0.05$) for any of these baseline characteristics (omnibus F-test).

[†] $p = 0.062$.

[‡] $p = 0.060$.

ple comparisons. All tests were two sided. Cox regression (4) was used with adjustment for baseline covariates to estimate relative hazards associated with the treatment groups and time-varying covariates such as smoking status and levels of inhaler compliance.

For additional detail on methods, see the online data supplement.

RESULTS

Selected baseline characteristics of LHS participants are shown in Table 1. There were no significant differences between groups. There were near-significant differences in sex, with the SI-A group having a smaller proportion of males (60.8%, $p = 0.062$) than the other two groups, and in marital status, with the SI-P group having the highest percentage of married participants (72.9%) and the UC group the lowest (69.5%, $p = 0.060$). Rates of contact at annual visits were quite high, ranging from 93% (Year 4) to 97% (Year 5), with no significant differences in contact rates between the groups. At the end of 5 years, a total of 18 of the 5,887 participants were lost to follow-up: six in SI-A, four in SI-P, and eight in UC.

Compliance rates are shown in Table 2. Groups SI-A and SI-P did not differ significantly in smoking category distribution, but there was a clear difference in smoking behavior between them and the UC group, with over 21% achieving sustained smoking cessation in the SI groups, versus only 5.4% in the UC group. Reciprocally, the number of continuing smokers was highest in the UC group.

There were no significant differences in inhaler use between the SI-A and SI-P groups, either in puffs per day or in overall compliance status. Those categorized as sustained satisfactory compliers (reporting using three or more puffs per day at each annual visit) comprised 33 to 34% of both groups. Approximately 44% were intermittently satisfactory compliers, whereas approximately 22% were continuing unsatisfactory compliers (fewer than three puffs per day at each annual visit).

Approximately 2.5% (149) of participants died during follow-up. Of these, approximately 25% died of CVD, and approximately two-thirds of the CVD deaths were due to CHD. Lung cancer was the cause of 38% of the deaths, whereas other cancers accounted for 22% (33 participants). Of the 5,887 participants, 754 were hospitalized at least once, and 282 were hospitalized at least twice. CVD accounted for 42% of the first hospitalizations and 48% of the second. CVD, cancer, and lower respiratory tract disease were the reasons for approximately 75% of all hospitalizations. CHD accounted for approximately two-thirds of total nonfatal CVD. In addition to the 57 deaths caused by lung cancer, 35 participants were diagnosed with the disease but survived to the end of follow-up. Hospitalization for lower respiratory disease was approximately one-third as common as for CVD.

Table 3 compares mortality and hospital morbidity among treatment groups and includes p values based on log-rank statistics. The "omnibus" p values represent tests of the hypothesis that the distributions of times to event are the same for all three groups. None of these reach conventional levels for statistical significance. However, there were differences between the SI-P group and the SI-A group, suggesting that SI-P group participants were at lower risk of cardiovascular death than those in the SI-A group. This was supported by pair-wise comparisons of the three groups using the log-rank test (Table 3). None of these differences would be significant if we adjusted the p values for the pair-wise comparisons for multiple testing. Table 3 does not demonstrate any meaningful difference between the SI-A and the UC groups. Figure 1 illustrates the time course of differences between the three treatment groups in fatal and nonfatal CVD events and supports the analytic results.

Multivariate analyses were undertaken to examine the effects of known and putative risk factors on morbidity and mortality among the study group as a whole. This allowed con-

TABLE 2. FINAL SMOKING STATUS AND FINAL INHALER COMPLIANCE STATUS, BY TREATMENT GROUP

| | SI-A | | SI-P | | UC |
|--|-------|------|-------|------|------|
| Overall Smoking Category* | | | | | |
| Sustained quitter, % | 21.1 | | 22.4 | | 5.4 |
| Intermittent quitter, % | 30.1 | | 28.6 | | 23.4 |
| Continuing smoker, % | 48.7 | | 49.0 | | 71.2 |
| Inhaler use at annual visits (puffs per day among visit attendees) | Mean | SD | Mean | SD | |
| Month 4 | 4.40 | 2.37 | 4.37 | 2.33 | – |
| Year 1 | 3.67 | 2.60 | 3.69 | 2.60 | – |
| Year 2 | 3.54 | 2.62 | 3.61 | 2.55 | – |
| Year 3 | 3.37 | 2.67 | 3.44 | 2.63 | – |
| Year 4 | 3.28 | 2.70 | 3.31 | 2.69 | – |
| Year 5 | 2.96 | 2.75 | 2.94 | 2.73 | – |
| Overall inhaler compliance status† | | | | | |
| Sustained satisfactory | 33.4% | | 34.0% | | – |
| Intermittent satisfactory | 43.5% | | 44.5% | | – |
| Continuing unsatisfactory | 23.1% | | 21.5% | | – |

Definition of abbreviations: SI-A = smoking intervention plus Atrovent; SI-P = smoking intervention plus placebo; UC = usual care.
 * There were no significant differences ($\alpha = 0.05$) in final smoking category between the Atrovent and placebo groups. Both smoking intervention groups differed significantly from the UC group on the final smoking category distribution ($p < 0.001$).
 † There were no significant differences ($\alpha = 0.05$) in final inhaler compliance status between the Atrovent and placebo groups.

sideration of smoking status of individual participants as well as treatment group assignment. Table 4 shows the results of Cox regression analyses for cardiovascular and respiratory disease. The results are presented in terms of the relative hazard of the events for specified increments in the explanatory variables, after adjustment for the other variables. Thus, an estimated relative hazard of larger than one implies that the specified increment in the covariate is associated with an increase in risk.

As expected, these analyses indicated that increasing age and diastolic blood pressure were risk factors for death from any cause and from CVD. A higher level of baseline 1-second forced expiratory volume was protective for both CHD and respiratory disease. Increased alcohol intake was protective for CVD but was associated with higher rates of respiratory disease. Increased body mass index was also a risk factor for respiratory illnesses, as was female sex. A higher level of education was associated with a lower risk of respiratory illnesses. Being married was associated with a higher risk of CHD, with similar trends in both sexes (but significant only in men). Smoking status (smoking or nonsmoking) at annual visits was entered in these analyses as a time-dependent covariate. The last line of Table 4 shows that smoking at annual visits was associated with 50 to 70% higher hazards of death, CVD, and CHD than not smoking.

Table 5 shows the numbers of specific earliest cardiovascular events resulting in hospitalization or death for participants in each of the three treatment groups. Fatal events, whether caused by CHD or other cardiovascular causes, were less common in the SI-P group than the others (SI-P versus SI-A, $p = 0.052$; SI-P versus UC, $p = 0.331$) and were slightly more common in the SI-A group than in the UC group ($p = 0.440$). Similar but smaller differences were evident for nonfatal CVD events, both those ascribed to CHD and to other CVD. Of the latter, there was a distinct preponderance of arrhythmia as a cause of hospitalization, but not of death, in the SI-A group, because of a relatively high prevalence of supraventricular tachycardia. There were nine people hospitalized with this type or arrhythmia in the SI-A group, as compared with two in the SI-P group and none in the UC group. The “other CVD” category of Table 5 represents a wide variety of cardiovascular conditions, including aneurysms, valve disorders, peripheral vascular diseases, and others. There was no obvious relationship between the treatment group and the frequency of any of these specific conditions.

The data of Tables 3 and 5 raise the question of real differences between the SI-A and SI-P groups in terms of CVD. The groups were not significantly different in terms of baseline risk factors and demonstrated similar changes in smoking behavior (Table 2), and thus, the most obvious potential cause

TABLE 3. FATAL AND NONFATAL EVENTS WITHIN 5 YEARS OF RANDOMIZATION, BY TREATMENT GROUP

| Event | SI-A (n = 1,961) | SI-P (n = 1,962) | UC (n = 1,964) | Omnibus p value* | Pair-wise Comparisons Unadjusted Nominal p Values* | | |
|------------------------------------|---------------------|---------------------|-------------------|---------------------|---|-------------------|-------------------|
| | | | | | SI-A versus SI-P | SI-A versus UC | SI-P versus UC |
| Death—any cause, n (%) | 54 (2.75) | 44 (2.24) | 51 (2.60) | 0.578 | 0.304 | 0.765 | 0.467 |
| CVD death, n (%) | 18 (0.92) | 7 (0.36) | 12 (0.61) | 0.084 | 0.027 | 0.271 | 0.250 |
| CHD death, n (%) | 12 (0.61) | 5 (0.25) | 8 (0.41) | 0.224 | 0.088 | 0.369 | 0.403 |
| Lung cancer death, n (%) | 18 (0.92) | 20 (1.02) | 19 (0.97) | 0.952 | 0.753 | 0.872 | 0.878 |
| Fatal/nonfatal CVD, n (%) | 136 (6.94) | 108 (5.50) | 129 (6.57) | 0.156 | 0.061 | 0.649 | 0.155 |
| Fatal/nonfatal CHD, n (%) | 85 (4.33) | 67 (3.41) | 83 (4.23) | 0.273 | 0.135 | 0.865 | 0.184 |
| Fatal/nonfatal lung cancer, n (%) | 31 (1.58) | 31 (1.58) | 30 (1.53) | 0.990 | 0.987 | 0.897 | 0.907 |
| Lower respiratory morbidity, n (%) | 37 (1.89) | 34 (1.73) | 45 (2.29) | 0.422 | 0.704 | 0.377 | 0.206 |

Definition of abbreviations: CHD = coronary heart disease; CVD = cardiovascular disease; SI-A = smoking intervention plus Atrovent; SI-P = smoking intervention plus placebo; UC = usual care.
 * All p values for group comparisons are based on the log-rank statistic without adjustment for other covariates.

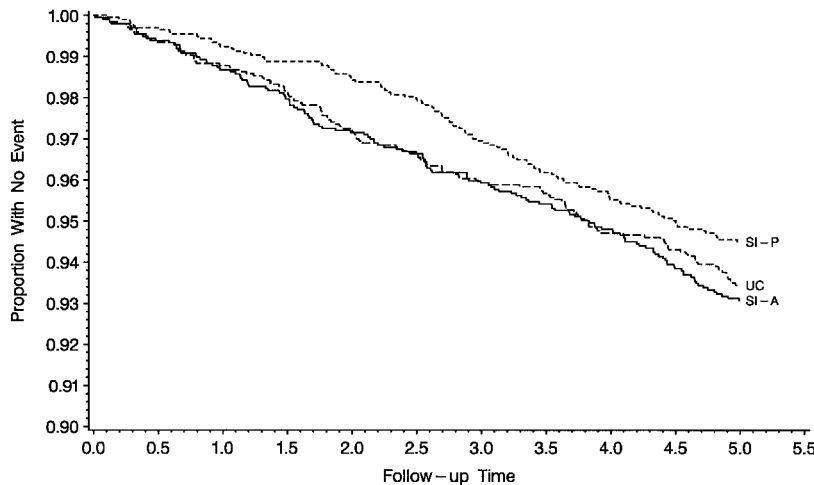


Figure 1. Proportions (± 2 SEM) of LHS participants free of fatal/nonfatal CVD through 5 years of follow-up, by treatment group.

of differences between them was the fact that SI-A participants were prescribed active bronchodilator and SI-P participants were prescribed placebo. If such were the case, that is, if bronchodilator were associated with an increase in CVD events, then one would expect the association to be stronger in the compliant participants, who actually took the bronchodilator, than in those who were noncompliant. Inhaler compliance was assessed on a 0–4 scale (*see METHODS*). Figure 2 shows compliance levels among participants with and without CVD events in the SI-A and SI-P groups. Participants in both treatment groups demonstrated similar compliance whether they had CVD events or not: No dose–response effect was evident. Similar analyses of all-cause mortality and fatal/nonfatal CVD yielded similar results. Two other analytic approaches also failed to show a dose–response relationship. These were Cox regression analyses of time to first cardiovascular or coronary event, with compliance entered as a time-dependent variable, and a proportional hazards analysis that examined active drug use at the visit immediately preceding cardiovascular events.

On the other hand, among SI-A participants with supraventricular tachycardia, compliance was unusually good; six of the nine SI-A participants with this kind of arrhythmia

were in compliance Level 4 at the time of hospitalization. In addition, one other, who developed her arrhythmia before compliance, was checked at her first follow-up visit and had definitely been using her inhaler.

DISCUSSION

The endpoints chosen—death and hospitalization—were carefully documented in a prospective fashion, and the associated diagnoses were assigned after review of records by an expert panel not involved in the conduct of the study and blinded to treatment group assignment. We analyzed these events in relationship to participant compliance. In the case of smoking, the data reported were validated by objective measurements and were quite reliable. Assessment of compliance with inhaler use depended on self-report, which very likely resulted in overestimates. We imputed nonuse of inhaler in the case of missed visits and found that results differed little whether one or two missed visits were required for this assumption. We also attempted to measure compliance by weighing inhaler canisters, but these data were incomplete and probably resulted in an underestimate, as people who did not return all

TABLE 4. COX MULTIPLE REGRESSION ESTIMATES OF RELATIVE HAZARDS FOR FIVE MORTALITY/MORBIDITY OUTCOMES, FOR SPECIFIED COMPARISONS OR INCREMENTS IN COVARIATES

| Covariate | Comparison or Increment | Death by Any Cause | CVD Death | Fatal or Nonfatal CVD | Fatal or Nonfatal CHD | Fatal or Nonfatal Respiratory Disease |
|---------------------------------|-------------------------|--------------------|-------------------|-----------------------|-----------------------|---------------------------------------|
| Treatment group | SI-A versus UC | 1.16 | 1.63 | 1.14 | 1.14 | 0.81 |
| | SI-P versus UC | 0.93 | 0.62 | 0.86 | 0.85 | 0.75 |
| Age | +10 Years | 2.29 [§] | 2.83 [§] | 2.16 [§] | 1.93 [§] | 1.07 |
| Sex | Male versus Female | 1.17 | 1.84 | 2.26 [§] | 3.82 [§] | 0.61 [†] |
| Baseline cigarettes per day | + 10 cigarettes | 1.06 | 1.17 | 1.07 [†] | 1.05 | 1.05 |
| BMI | + 3 kg/m ² | 0.92 | 0.80 | 1.07 | 1.09 | 1.31 [§] |
| Diastolic BP | + 10 mm Hg | 1.33 [†] | 1.50 [†] | 1.23 [§] | 1.27 [‡] | 0.84 |
| Alcoholic drinks per week | + 5 drinks | 1.07 | 1.01 | 0.87 [‡] | 0.86 [†] | 1.18 [†] |
| Education, yrs | + 4 years | 0.87 | 0.80 | 0.91 | 0.94 | 0.66 [‡] |
| Race | Nonwhite versus white | 1.32 | 1.13 | 1.20 | 0.95 | 1.46 |
| Marital status | Married versus not | 0.90 | 0.85 | 1.35 [*] | 1.60 [‡] | 0.73 |
| FEV ₁ % predicted | + 10% | 0.88 | 0.78 | 0.95 | 0.84 [†] | 0.72 [§] |
| Smoking status at annual visits | Smoking versus not | 1.48 [*] | 1.81 | 1.50 [‡] | 1.71 [‡] | 1.00 |

Definition of abbreviations: BMI = body mass index; BP = blood pressure; CHO = coronary heart disease; CVD = cardiovascular disease; FEV₁ = forced expiratory volume at 1 second; SI-A = smoking intervention plus Atrovent; SI-D = smoking intervention plus placebo; UC = usual care.

*0.05, < p ≤ 0.10.

[†]0.01, < p ≤ 0.05.

[‡]0.001, < p ≤ 0.01.

[§]p ≤ 0.001.

TABLE 5. NUMBERS OF FIRST CARDIOVASCULAR EVENTS, BY TREATMENT GROUP

| First Cardiovascular Events | SI-A (n = 1,961) | | SI-P (n = 1,962) | | UC (n = 1,964) | |
|--|------------------|------|------------------|------|----------------|------|
| All events, n (%) | 136 | 6.94 | 108 | 5.50 | 129 | 6.57 |
| Fatal CVD events, n (%) | 15 | 0.76 | 6 | 0.31 | 11 | 0.56 |
| CHD, n (%) | 9 | 0.46 | 4 | 0.20 | 7 | 0.36 |
| Myocardial infarction, n (%) | 3 | 0.15 | 2 | 0.10 | 3 | 0.15 |
| Ischemic heart disease, n (%) | 2 | 0.10 | 1 | 0.05 | 0 | 0.00 |
| Sudden cardiac death, n (%) | 4 | 0.20 | 1 | 0.05 | 4 | 0.20 |
| Other cardiovascular events (non-CHD), n (%) | 6 | 0.31 | 2 | 0.10 | 4 | 0.20 |
| Arrhythmia, n (%) | 0 | 0.00 | 0 | 0.00 | 1 | 0.05 |
| Pulmonary embolism, n (%) | 1 | 0.05 | 0 | 0.00 | 0 | 0.00 |
| Stroke, n (%) | 2 | 0.10 | 1 | 0.05 | 1 | 0.05 |
| Other CVD, n (%) | 3 | 0.15 | 1 | 0.05 | 2 | 0.10 |
| Nonfatal CVD events, n (%) | 121 | 6.17 | 102 | 5.20 | 118 | 6.01 |
| CHD, n (%) | 73 | 3.72 | 61 | 3.10 | 70 | 3.62 |
| Myocardial infarction, n (%) | 41 | 2.09 | 29 | 1.48 | 30 | 1.53 |
| Angina, n (%) | 4 | 0.20 | 2 | 0.10 | 2 | 0.10 |
| Ischemic heart disease, n (%) | 27 | 1.38 | 28 | 1.43 | 38 | 1.93 |
| Coronary revascularization, n (%) | 1 | 0.05 | 0 | 0.00 | 1 | 0.05 |
| Other CHD, n (%) | 0 | 0.00 | 2 | 0.10 | 0 | 0.00 |
| Other cardiovascular events (non-CHD), n (%) | 48 | 2.45 | 41 | 2.09 | 47 | 2.39 |
| Arrhythmia, n (%) | 11 | 0.56 | 3 | 0.15 | 3 | 0.15 |
| Transient ischemic attack, n (%) | 3 | 0.15 | 2 | 0.10 | 5 | 0.25 |
| Congestive heart failure, n (%) | 2 | 0.10 | 2 | 0.10 | 3 | 0.15 |
| Hypertension, n (%) | 0 | 0.00 | 1 | 0.05 | 0 | 0.00 |
| Pulmonary embolism, n (%) | 3 | 0.15 | 4 | 0.20 | 2 | 0.10 |
| Stroke, n (%) | 7 | 0.36 | 6 | 0.31 | 3 | 0.15 |
| Other CVD (non-CHD), n (%) | 22 | 1.12 | 23 | 1.17 | 31 | 1.58 |

Definition of abbreviations: CHD = coronary heart disease; CVD = cardiovascular disease; SI-A = smoking intervention plus Atrivent; SI-P = smoking intervention plus placebo; UC = usual care.

canisters were judged to be noncompliant whether they used their inhalers or not. Annual follow-up visit rates were very high; there were few missing data.

At baseline, LHS participants were middle-aged with substantial tobacco exposure and mild to moderate airways obstruction. Smokers with the highest risk for short-term cardiovascular events were excluded. Given this profile, the relatively low subsequent mortality and morbidity were not surprising. Approximately two-thirds of the deaths during follow-up were caused by lung cancer or CVD, with CHD being the most important component of the latter. The majority of hospitalizations was ascribed to these diseases as well; hospitalizations caused by airway obstruction were less common because pulmonary function was not severely compromised. Baseline risk factors for death or hospitalization (Table 4) were similar to those reported elsewhere. Events caused by CHD were positively associated with age, male sex, the married state, higher diastolic blood pressure, and poor pulmonary function. Alcohol consumption was protective. Of interest was the fact that smoking cessation during the 5-year study was associated with reduced mortality and morbidity for CVD and CHD. Clearly, the effects of smoking cessation on CHD were evident in a relatively short time, an observation also made in the Multiple Risk Factor Intervention Trial (5, 6). This contrasts with the data for lung cancer; smoking cessation did not reduce lung cancer incidence within the limited duration of the LHS, also in agreement with results from the Multiple Risk Factor Intervention Trial (5). Hospitalization for disease of the lower respiratory tract was associated with poor pulmonary function but also with alcohol consumption and the female sex. Education was protective, but smoking status after the start of the study did not influence hospitalizations for respiratory disease significantly.

There were no clearly significant differences in mortality or hospitalizations between the UC group and either of the two special intervention groups, although there was greater smoking

cessation and a slower rate of decline of lung function in the latter two groups. This was probably because the follow-up period was relatively short and the cohort was middle-aged, and the rate of sustained cessation was only approximately 16% higher in the smoking intervention groups than in the UC group.

The most striking intergroup differences in mortality and morbidity (Tables 3 and 5) were between the SI-A and SI-P groups. Differences that reached or approached nominal significance were observed in deaths caused by CVD and coronary artery disease and total deaths and hospitalizations caused by CVD. This raises the important and unanticipated possibility that ipratropium bromide, the inhaled bronchodilator used in the LHS, somehow caused these untoward events. Ipratropium bromide has been widely used, especially in chronic obstructive pulmonary disease, for at least 10 years with no evidence of such untoward events (7-9). Indeed, it is regarded as virtually without systemic side-effects, at least in the short term, as very small amounts of the drug are absorbed subsequent to inhalation (9, 10). On the other hand, the LHS may have been uniquely well qualified to detect side-effects in that it followed a large group of users very closely over a relatively long period of time. To be entirely credible, putative side-effects should be statistically significant and dose related. The cardiovascular events and/or deaths apparently associated with ipratropium did not fulfill these criteria. Although differences between SI-A and SI-P approached statistical significance, they were not consistently significant, and the tests used were not adjusted for multiple tests and endpoints, and such adjustment would have rendered all results nonsignificant. Although we sought a dose effect in several ways, we were unable to demonstrate one; the risk of cardiovascular events or deaths was not higher in members of the SI-A group who reported ipratropium use than in those who did not. Thus, we were unable to develop strong evidence that the differences between the SI-A and SI-P groups in coronary and cardiovascular events and deaths were a drug effect. On the

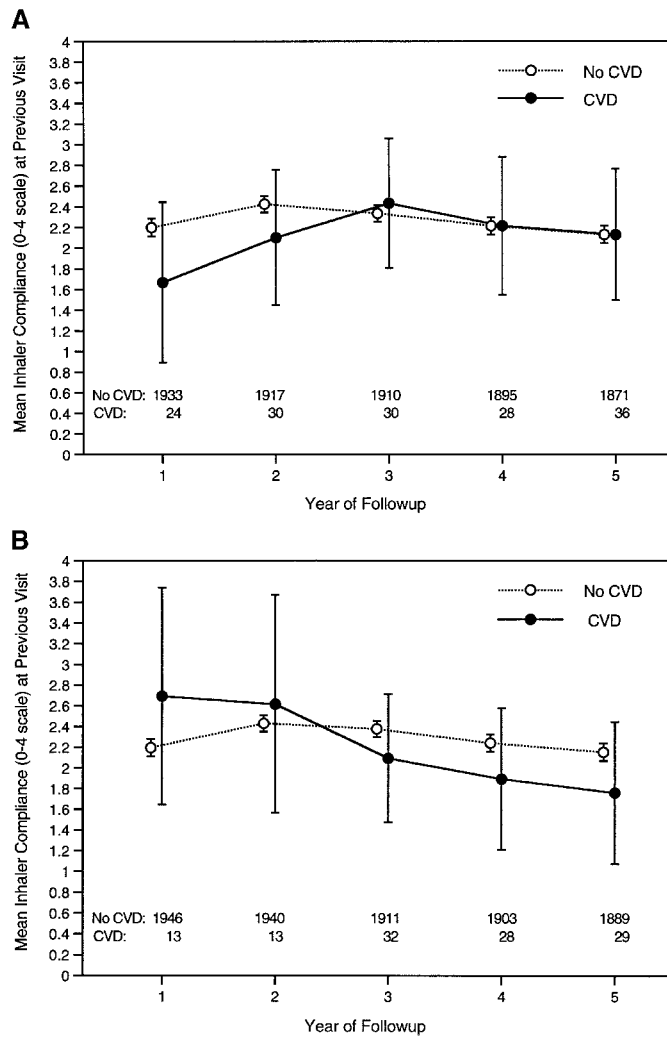


Figure 2. Mean inhaled compliance (0–4 scale) at visits preceding occurrence of fatal or nonfatal CVD. (A) SI-A participants. (B) SI-P participants.

other hand, we cannot exclude such an effect, and it is clear that the LHS was underpowered in terms of detecting one.

The rationale behind our decision not to adjust for multiple testing is the following: adjusting has the desirable effect of decreasing the overall rate of false positives but also increases the overall rate of false negatives. We have observed a pattern of outcomes that is consistent with the hypothesis that use of ipratropium bromide may be associated with an increased risk of cardiovascular events, but do not prove that hypothesis. Additional studies to refute or confirm our findings or to investigate possible mechanisms may be warranted. Adjustment for multiple testing would have resulted in nonsignificance of all p values and would have obscured findings that may be deserving of additional study.

There have been several recent studies of untoward events associated with bronchodilator therapy. A database study of β agonists suggested that in patients with CVD, starting treatment with these drugs was associated with an increased risk for myocardial infarction (11); the nature of the study precluded assessment of causality, and there were few cases noted. Of perhaps greater interest is a recent retrospective case control study of British patients who had been hospitalized with asthma that found that postdischarge ipratropium prescriptions were associated with increased mortality (12). The association was not significant for car-

diovascular deaths after appropriate adjustments but was significant for deaths ascribed to asthma and chronic obstructive pulmonary disease. It may well be that the prescription of ipratropium was simply a surrogate for the presence or severity of chronic obstructive pulmonary disease, however (12). A subsequent large database study found no credible association between ipratropium therapy and mortality in either patients with asthma or patients with chronic obstructive pulmonary disease (13).

On the other hand, nine of our SI-A participants were hospitalized for supraventricular tachycardia as compared with two in the SI-P group and none in the UC group. Supraventricular tachycardia is perhaps a credible side-effect of ipratropium. If the agent was absorbed, it might give rise to such arrhythmias by virtue of its anticholinergic properties; intravenous ipratropium administration has caused tachycardia in humans (14). Furthermore, there was evidence of a dose effect. The SI-A participants who had supraventricular tachycardias were unusually compliant; seven of the nine reported using their inhalers during the period that they developed the arrhythmia, and six were classified as highly compliant, having reported using four or more puffs of ipratropium daily. This was much greater than the 33% adherence to three puffs a day in the SI-A group as a whole (Table 2). Against the idea of ipratropium causing arrhythmias is the evidence that there is very little systemic absorption of inhaled drug (9, 10), but it is extremely difficult to prove that this never occurs. Thus, the excess hospitalizations for supraventricular tachycardia in the SI-A group may represent a drug effect. It must be noted, however, that such a drug effect should not be regarded as proven.

In summary, mortality and morbidity were not high in the LHS because the participants were healthy volunteers with only mild to moderate lung function impairment caused by smoking. There were no significant differences among the original treatment groups for the common causes of morbidity and mortality such as CVD, including CHD, lung cancer, and respiratory disease. However, there was an unexpected tendency for coronary and CVD to be more common among SI-A participants than SI-P participants. We were unable to demonstrate a dose-effect for major disease categories but did note a preponderance of supraventricular tachycardia in the SI-A group that was apparently dose-related and that may be a credible side-effect of ipratropium bromide.

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APPENDIX

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