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Prospective Study of Inhaled Corticosteroid Use, Cardiovascular Mortality, and All-Cause Mortality in Asthmatic Women*

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Abstract

Background—Therapy with inhaled corticosteroids (ICSs) decreases the risk of asthma exacerbations. Recent studies have suggested that ICS therapy also may decrease the risk of cardiovascular disease, and perhaps of all-cause mortality. We examined this hypothesis in a large, well-characterized cohort of asthmatic women.

Methods—In 1976, the Nurses' Health Study enrolled 121,700 registered nurses, who were 30 to 55 years of age. Participants were asked about "physician-diagnosed asthma" on biennial questionnaires. In 1998, asthmatic participants were sent a supplementary questionnaire on asthma diagnosis and management, including ICS use. Mortality was assessed through 2003, without knowledge of the 1998 (baseline) ICS status. The odds ratios (ORs) for death were adjusted for age, asthma severity, smoking, heart disease, cancer, stroke, aspirin, and statin use.

Results—Among 2,671 eligible women (*ie*, those who responded to the 1998 supplement [85%], met criteria for persistent asthma, and had not received a prior diagnosis of COPD), 54% reported ICS use. Over the next 5 years, 87 women (3.3%) died (cardiovascular deaths, 22; cancer deaths, 31; other, 34 [including 4 from asthma]). Compared to asthmatic women who did not use ICSs, those receiving therapy with ICSs had lower all-cause mortality (OR, 0.58; 95% confidence interval [CI], 0.36 to 0.92). ICS users were at significantly lower risk of cardiovascular death (OR, 0.35; 95% CI, 0.13 to 0.93), but not of death from cancer (OR, 0.66; 95% CI, 0.32 to 1.38) or other causes (OR, 0.62; 95% CI, 0.30 to 1.27).

Conclusions—ICS use was associated with significantly lower cardiovascular and all-cause mortality in women with asthma. These observational data suggest that ICSs may indeed have antiinflammatory benefits beyond the airway, which is a possibility that merits further study.

Keywords

all-cause mortality; asthma; cardiovascular mortality; inhaled corticosteroids

Asthma affects approximately 7% of US adults, with an annual cost of almost $20 billion.[1] Airway inflammation underlies this chronic disease and, for that reason, antiinflammatory treatments are a major part of disease management.[2] Inhaled corticosteroids (ICSs) are widely

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recognized as the "preferred" antiinflammatory treatment for individuals with persistent asthma, a group that constitutes most people with asthma.[2]

Although ICSs are known to improve lung function and decrease asthma exacerbations, epidemiologic studies have suggested other, nonpulmonary benefits. For example, ICS usage has been linked with lower all-cause mortality among elderly individuals with asthma,[3] and with lower risk of myocardial infarction in a younger population.[4] Although neither study could adjust for potential confounding by important lifestyle factors (*eg*, smoking), the hypothesized benefits received indirect support from randomized trial evidence that ICS treatment lowers levels of systemic markers of inflammation such as serum C-reactive protein (CRP).[5] Given the important role of systemic inflammation in patients with cardiovascular disease,[6] the CRP finding provided a compelling mechanism whereby ICS use might decrease the risk of cardiovascular disease and thereby yield all-cause mortality benefits in older populations. To further explore this hypothesis, we examined the relation of ICS usage to all-cause mortality, including cardiovascular mortality, in a large cohort of older women with asthma.

Methods and Materials

In 1976, the Nurses' Health Study[7] enrolled 121,700 married, female registered nurses, aged 30 to 55 years, who resided in 1 of 11 states in the United States, and who completed a mailed questionnaire on hormone use and medical history. We have updated the information with biennial follow-up questionnaires and have inquired about a physician diagnosis of asthma since 1988. To date, the follow-up of the original cohort has consistently been > 90%. The project has institutional review board approval, with all participants providing informed consent.

Definition of Asthma

During follow-up through 1996, a total of 10,496 women reported a physician diagnosis of asthma.[8] In 1998, we sent supplemental questionnaires to collect detailed information on respiratory symptoms and medication use to all of these participants, excluding those who had died (n = 437) or had either withdrawn from the study or were lost to follow-up (n = 223). Of 9,836 recipients who were sent questionnaires, 163 had died and 8,197 responded (85%).

To improve the accuracy of the asthma diagnosis, we excluded participants with other pulmonary diseases, such as sarcoidosis. We also excluded the 3,257 women who reported COPD, including physician-diagnosed chronic bronchitis or emphysema. We have previously validated self-reported COPD diagnosis against medical records in this cohort of registered nurses.[9] The COPD exclusion also was motivated by the fact that ICS therapy was not commonly used in the management of COPD in 1998; the exclusion decreases the potential for intractable confounding by disease severity.[10]

For similar reasons, we also excluded the 1,968 nurses with "mild intermittent" asthma using criteria based on national asthma guidelines[11] and developed in earlier work by our group.[8] ICS therapy is not recommended for these asthma patients;[2,11] therefore, this exclusion left only participants with persistent asthma, which is an established indication for ICS usage. The case definition for "persistent" asthma in the present study required a report of a physician diagnosis of asthma on the regular questionnaire (1988 to 1996) that was repeated on the supplementary questionnaire (1998), plus the use of an asthma controller medication (*eg*, inhaled or systemic corticosteroid, theophylline, leukotriene modifier, or cromolyn) in the 12-month period before administration of the supplemental questionnaire. We have validated the self-reported incidence of asthma against medical records for a random sample of 100 cases in a related study of female nurses and confirmed that all carried a physician diagnosis of

asthma. Moreover, 91 patients had strong, consistent evidence for asthma, 4 patients had transient asthma, and 5 patients had some evidence of a questionable diagnosis.[12] Thus, there were 2,671 eligible women with doctor-diagnosed asthma of persistent severity, who were using at least one asthma controller medication and were without other pulmonary disorders at the 1998 start of this longitudinal study.

Ascertainment of ICS Use and Covariates

The 1998 supplementary questionnaire asked about asthma diagnosis, current treatment, and symptoms. Nurses were asked about medication usage in the year before responding to the supplementary questionnaire, including treatment with ICSs and other common asthma medications. The questionnaire did not collect information on ICS dosage, refill rate, or other aspects of medication usage.

Baseline covariates in 1998 included age, persistent asthma severity (*ie*, mild, moderate, or severe per the National Asthma Education and Prevention Program guidelines[11]), and smoking status (*ie*, never, past, or current). Given our primary focus on all-cause mortality, we also included any personal history of the following three major causes of mortality in US adults: heart disease; cancer (except nonmelanoma skin cancer); and stroke.[13] Finally, we included 1998 usage of aspirin or statins, which are long-term medications that might confound the association between ICS usage and mortality.

Mortality Outcomes

The mortality follow-up for this analysis began in 1998 and continued through 2003. Deaths were reported by next of kin, coworkers, or postal authorities, or were ascertained by searching the National Death Index for participants who did not respond. In accordance with established protocols, nonresponding participants were assumed to be alive if they were not listed in the National Death Index. Study physicians reviewed death certificates to assign cause of death. For major causes of cancer or cardiovascular death, study physicians also reviewed medical records or autopsy reports. Mortality data were processed without knowledge of ICS therapy status. The mortality follow-up was > 99% complete throughout the study period.

Statistical Analysis

Given the very low attrition rate, and the rarity of the primary outcome (*ie*, all-cause mortality) during the 5-year follow-up period, the association between ICS usage and mortality was examined using multivariate logistic regression. Odds ratios (ORs) are reported with 95% confidence intervals (CIs). At the onset of model building, all covariates were chosen *a priori* based on their association with asthma or all-cause mortality; all covariates were entered as indicator variables. All p values were two-tailed, with $p < 0.05$ considered to be statistically significant. Analyses were performed using a statistical software package (SAS, version 8.2; SAS Institute; Cary, NC).

Results

Among 2,671 eligible women with persistent asthma, approximately half (54%) reported ICS use. Table 1 shows the baseline characteristics of the study population, by ICS status. The exposed group (the ICS group) and nonexposed group (the no ICS group) were similar. Despite the exclusion of women with a known diagnosis of COPD, approximately half of these older women, in both groups, were past or current smokers, with an average smoking history of 20 pack-years.

Over the next 5 years, 87 women (3.3%) died. By major category of death, 22 deaths were from cardiovascular causes, 31 deaths were from cancer (including 3 patients with lung cancer),

and 34 deaths from other causes (including four patients with fatal asthma); the other group included patients with 18 separate conditions. Among the women with asthma who were not receiving ICS therapy in 1998, there were 51 deaths (4.2%). Among women who were receiving ICS therapy in 1998, only 36 (2.5%) died. This absolute mortality difference of 1.7% (95% CI, 0.3 to 3.1%) translates into an unadjusted risk ratio of 0.60 (95% CI, 0.39 to 0.91).

The significantly lower all-cause mortality of asthmatic women receiving ICS therapy persisted in several multivariate models (Table 2). Further adjustment for the number of pack-years of smoking, other cardiovascular risk factors (*ie*, history of hypertension, history of diabetes, and family history of myocardial infarction), or socioeconomic status (as measured by the husband's educational attainment) did not change the results (data not shown). The approximately 40% reduction in all-cause mortality was mediated by an even larger, statistically significant reduction in cardiovascular mortality (OR, 0.35; 95% CI, 0.13 to 0.93). By contrast, ICS usage was not significantly associated with death from cancer or other causes.

Although the statistical power was limited, a secondary analysis that restricted the cohort to never-smokers or women with a smoking history of < 20 pack-years produced qualitatively similar results for all-cause mortality (61 deaths; age-adjusted and severity-adjusted OR, 0.68; 95% CI, 0.40 to 1.17), cardiovascular mortality (15 deaths; adjusted OR, 0.33; 95% CI, 0.10 to 1.12), and noncardiovascular mortality (46 deaths; adjusted OR, 0.82; 95% CI, 0.44 to 1.50).

DISCUSSION

During 5 years of follow-up of 2,671 asthmatic women in the Nurses' Health Study,[7] the baseline usage of ICSs was associated with significantly lower all-cause mortality. The observed decrease was mediated by an even larger difference in cardiovascular mortality between ICS users and nonusers. The apparent nonpulmonary benefits of ICS therapy were not materially affected by controlling for a variety of potential confounders. Thus, our findings support and extend the results of two epidemiologic studies from Canada.[3,4]

The first study, by Sin and Tu,[3] examined the relation of ICS usage to all-cause mortality. The authors identified a cohort, age ≥ 65 years, who had been hospitalized for asthma and then linked this database with other administrative data. Although the study may include immortal time bias, the authors found that ICS users had lower all-cause mortality over the ensuing year after hospital discharge (hazard ratio, 0.61; 95% CI, 0.47 to 0.80). The use of administrative data precluded adjustment for potentially important differences according to ICS therapy status.

Shortly thereafter, Suissa and colleagues[4] reported an inverse association between ICS usage and myocardial infarction. The authors identified a population-based cohort of asthmatic subjects, ages 5 to 44 years, and found that ICS users had a lower risk of myocardial infarction (risk ratio, 0.56; 95% CI, 0.32 to 0.99). The apparent benefit was greater among individuals with more severe asthma and was not explained by the differential use of bronchodilators. Again, the study was limited by the lack of information on potentially important confounders, such as smoking. The authors called for future studies in older individuals with asthma.

National guidelines[2] have designated ICS therapy as the preferred treatment for asthma because of its beneficial effects on asthma control. Although mortality benefits might have been predicted as a result of the known beneficial effect of ICS therapy on the risk of fatal asthma,[14] exacerbations of this extreme severity are quite rare[1]; the vast majority of asthmatic individuals will not die of their asthma. The most likely cause of death for older women with asthma is the same as that for other adults in industrialized societies, cardiovascular disease.[13] Interestingly, there is a growing literature on the association between systemic inflammation (as measured by serum CRP levels) and cardiovascular disease.[6] Indeed, several effective

medications for the treatment of coronary heart disease, such as statins, are thought to exert their cardioprotective effects, at least in part, through reductions in serum CRP levels.[15]

In 2004, Sin and colleagues[5] reported that ICS therapy may provide a similar CRP benefit for those patients with respiratory disease. The authors performed a randomized, double-blind, placebo-controlled trial involving 41 patients with mild-to-moderate COPD to examine the effects of ICS therapy on systemic inflammation. The withdrawal of ICS therapy increased baseline CRP levels by 71%, while a return to ICS therapy for 2 weeks reduced CRP levels by 50%. No significant changes were observed with placebo. An additional 8 weeks of ICS therapy was associated with CRP levels that were lower than those at baseline (29% reduction). Interestingly, 2 weeks of prednisone therapy reduced CRP levels by a comparable amount (63%) to that of ICS therapy, even though the ICS dosage (fluticasone, 500 μg bid) was thought to be too low to mimic the effects of therapy with systemic corticosteroids.

The finding for prednisone therapy led the authors to speculate that ICS therapy might affect CRP production indirectly by down-regulating the expression of certain cytokines produced in the airways (*eg*, interleukin-6, which is a major signaling cytokine for CRP expression by hepatocytes). Interleukin-6 levels are elevated in both COPD patients (*eg*, those studied by Sin et al[5]) but also among adults with asthma.[16] Likewise, serum CRP levels are elevated among asthmatic individuals,[17,18] especially during exacerbations.[19] These observations provide a plausible mechanism for how ICS usage could decrease the risk of cardiovascular mortality and, consequently, all-cause mortality.

Given the difficulty of using observational data to evaluate the effects of treatment, we sought randomized trial data to better understand our epidemio-logic findings and those of other investigators.[3,4] Although randomized trials with ICS-mortality data are not readily available from asthmatic populations, there are a few COPD studies of potential relevance. The comparison is complicated, of course, by differences in the quality and quantity of inflammation in COPD, compared to asthma, along with COPD patients' inherently higher mortality rate.[20] These differences may help to explain the apparent lack of cardiovascular benefit from ICS usage in the Towards a Revolution in COPD Health (or TORCH) trial.[21] In that 3-year, randomized, placebo-controlled trial of patients with moderate-to-severe COPD, patients receiving ICS therapy had a statistically similar rate of cardiovascular death (4%) as those receiving placebo (5%).

More relevant data may come from studies of patients with mild COPD, a population that better resembles older individuals with asthma. Löfdahl and colleagues[22] reported a *post hoc* analysis of ICS usage and cardiovascular outcomes in this group with milder asthma, using data from a 3-year randomized, double-blind, placebo-controlled trial. Among the 1,175 study subjects, those assigned to the ICS intervention had a significantly lower incidence of ischemic cardiac events (18 of 593 subjects; 3.0%) than those assigned to receive placebo (31 of 582 subjects; 5.3%). Thus, there may be a COPD severity level beyond which ICS benefits, if truly causal, are not observed.

Our study has several potential limitations. Since ICS status was not randomly assigned to cohort participants, unadjusted confounding is an alternative explanation for the results. In our study, all participants had a clear indication for ICS treatment (persistent asthma), and the disease severity was indeed higher among those receiving ICSs (Table 1); the impact of this observation is uncertain, but it might bias the effect of ICS therapy toward the null. Unfortunately, further analysis by ICS dose or duration is not possible. Another limitation relates to the relative homogeneity of the study participants. In addition to being composed only of women, the cohort was > 90% white, and all participants were married registered nurses at the time of study enrollment. Although this might be seen as a limitation in terms of

generalizability, the relative homogeneity of the cohort was a major strength when examining mortality, which often is intractably confounded by socioeconomic status and other difficult-to-measure factors. Nevertheless, even if our inferences are correct for women, who account for the majority of asthmatic adults,[1] our results will need to be replicated in longitudinal studies of more diverse populations, and preferably in randomized trials.

Although the all-cause mortality status is unequivocal, we acknowledge that the classification of cause of death is challenging. We followed the established protocols of the Nurses' Health Study[7] for coding both cardiovascular and cancer deaths. Nevertheless, it remains possible that some of the more sudden "cardiovascular" deaths may actually represent fatal, sudden-onset asthma exacerbations[23] or an interaction between these two conditions. Either way, the all-cause mortality findings suggest a net benefit. Likewise, we note the existence of reports that ICS usage may decrease cancer risk.[24,25] While the all-cause mortality finding was mediated by cardiovascular deaths, we cannot exclude that ICS therapy may have a more modest beneficial (or harmful) effect on cancer mortality (OR, 0.66; 95% CI, 0.32 to 1.38). This possibility will need to be addressed in larger studies that focus on cancer outcomes.

In summary, we found significantly lower cardiovascular and all-cause mortality among older asthmatic women who used ICSs compared to comparable women who did not use ICSs. These observational data suggest that ICS therapy may indeed have antiinflammatory benefits beyond the airway, which is a possibility that merits further study. Although a randomized trial of ICS vs non-ICS treatment is unlikely to happen in the near term due to ethical concerns regarding the nontreatment of patients with persistent asthma with ICSs, the next steps include the replication of our findings in other cohorts and mechanistic trials of the extrapulmonary, antiinflammatory effects of ICS therapy. Although pulmonary benefits (*eg*, improved lung function and decreased risk of exacerbation) would remain the primary reasons for using ICSs, the confirmation of all-cause mortality benefits would help with physician prescribing for, and medication adherence by, older adults with asthma. The long-term value of the early initiation of ICS therapy may go well beyond improved asthma control.[2]

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Abbreviations

CI
: confidence interval

CRP
: C-reactive protein

ICS
: inhaled corticosteroid

OR
: odds ratio

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Table 1

Baseline Characteristics of Women With Persistent Asthma in the Nurses' Health Study, According to ICS Status (1998)*

Characteristics	Receiving ICSs (n = 1,448)	Not Receiving ICSs (n = 1,223)
Age, yr	62 ± 7	63 ± 7
Asthma severity		
Mild persistent	47	52
Moderate persistent	42	44
Severe persistent	12	4
Smoking		
Never	48	49
Past	48	43
Current	3	8
History,† pack-yr	18 ± 18	22 ± 22
History of heart disease	3	3
History of cancer	14	13
History of stroke	2	2
Aspirin frequency		
< 3 d/mo	64	57
1–4 d/wk	9	11
> 5 d/wk	19	23
Missing	8	9
Statin use	13	15

*Values are given as the mean ± SD or %.

†Among current and past smokers only.

Table 2

Association Between ICS Usage and Subsequent Mortality Among 2,671 Women With Persistent Asthma, by Major Category of Death (1998–2003)*

	Mortality			
Variables	**All-Cause**	**Cardiovascular**	**Cancer**	**Other**
Deaths	87	22	31	34
Participants	2,671	2,606	2,615	2,618
Adjustments				
Age	0.63 (0.41–0.98)	0.43 (0.17–1.07)	0.72 (0.35–1.47)	0.71 (0.36–1.41)
Age and severity	0.57 (0.36–0.90)	0.36 (0.14–0.96)	0.69 (0.33–1.44)	0.60 (0.29–1.23)
Age, severity, and smoking	0.59 (0.37–0.93)	0.37 (0.14–0.98)	0.69 (0.33–1.44)	0.60 (0.29–1.24)
Multivariate†	0.58 (0.36–0.92)	0.37 (0.14–0.99)	0.66 (0.32–1.38)	0.62 (0.30–1.27)

*Values are given as No. or OR (95% CI).

†The multivariate models for all-cause and cardiovascular mortality are adjusted for age, persistent asthma severity, smoking status, history of heart disease, history of cancer, history of stroke, aspirin frequency, and statin use. The multivariate models for cancer and other mortality are adjusted for all factors above except history of heart disease.