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Low-dose inhaled corticosteroids and the risk of acute myocardial infarction in COPD

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ABSTRACT: **Inflammation plays a major role in the development and complications of atherosclerosis. Here, the dose-related impact of inhaled corticosteroids (ICS), used for their anti-inflammatory properties, on the risk of acute myocardial infarction (AMI) is studied in a cohort of chronic obstructive pulmonary disease (COPD) patients.**

Saskatchewan (Canada) health services databases were used to form a population-based cohort of 5,648 patients, ⩾55 yrs, who received a first treatment for COPD between 1990 and 1997. A nested case-control analysis was conducted, where 371 cases presenting with a first AMI were matched with 1,864 controls, based on the date of cohort entry and age. A conditional logistic regression was used to estimate the effect of ICS, after adjusting for use of oral corticosteroids, severity of COPD, sex, systemic hypertension, diabetes and cardiovascular disease.

ICS were used in the prior year by 42.2% of cases and 46.4% of controls. Overall, current use of ICS was not associated with a significant decrease in the risk of AMI. However, a 32% reduction in the risk of AMI was observed for doses ranging 50–200 $\mu g \cdot day^{-1}$.

In conclusion, very low doses of inhaled corticosteroids may be associated with a reduction in the risk of acute myocardial infarction.

KEYWORDS: **Acute myocardial infarction, chronic obstructive pulmonary disease, cohort study, databases, inflammation, inhaled corticosteroids**

Chronic obstructive pulmonary disease (COPD) is characterised by slowly progressive and, mostly, irreversible airflow limitation [1]. Inflammatory changes in the airway and lung parenchyma are considered to be responsible for the decline in lung function. As COPD and asthma share common disease features, and because corticosteroids are effective in treating airway inflammation in asthma, these medications are now widely used in the treatment of COPD [2, 3]. Corticosteroids, however, are known to promote hypertension, hyperlipidaemia and glucose intolerance [4–6], well-recognised risk factors for cardiovascular disease. Since the effect of corticosteroids on the cardiovascular system is dose related, the low doses contained in inhaled corticosteroids (ICS) are thought to have few, if any, cardiovascular side-effects.

Inflammation plays a major role in the initiation and progression of coronary atherosclerotic plaque [7] and its complications, such as acute coronary syndromes [8–10]. In clinical studies, markers of inflammation, such as C-reactive protein, were found to predict the risk of future myocardial infarction [11, 12]. It has, therefore, been suggested that anti-inflammatory agents may prevent cardiovascular disease [13] and that the risk reduction observed with aspirin may also be due to its anti-platelet effect [11]. Despite limited systemic side-effects, ICS possess systemic anti-inflammatory properties [14]. It is, therefore, possible that ICS might also prevent acute coronary syndromes. Indeed, a recent study showed a protective effect of ICS on the risk of acute myocardial infarction (AMI) in a population of asthma patients [15].

Therefore, in this study, the effect of ICS on the risk of AMI was evaluated in a population-based sample of COPD patients. It was hypothesised that the effect of ICS was dose related, specifically, that a protective effect was attained at doses large enough to have a systemic effect, yet small enough to not induce side-effects.

METHODS

Source of data and population

The Health Insurance Databases of Saskatchewan (Canada) constituted the primary source of data.

For editorial comments see page 589.

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These databases include all residents eligible for health coverage (~1,000,000). Approximately 9% of the population have their drug prescriptions paid by another agency and are, therefore, not eligible for outpatient prescription drug benefits [16]. These databases have been used extensively for research, and provide valid information for each individual on prescriptions dispensed, hospital stay, use of physician services and vital status information. The recording of cardiovascular diseases in the hospital separation database has been previously studied and found to be accurate [17]. Subjects cannot be identified nor be contacted to obtain supplemental information.

A population-based cohort of new patients with COPD was defined according to the drugs dispensed: to enter the cohort, a minimum of three prescriptions was required, on two different dates, in any 1-yr period, of an inhaled or oral β_2-agonist, xanthine or ipratropium (grouped under the term bronchodilators). The entry date was the time of the third prescription for a bronchodilator between January 1, 1990, and December 31, 1997. Patients $\geqslant$55 yrs at cohort entry, who had not received any bronchodilator, anti-asthma drug (cromolyn, nedocromil or ketotifen), or nasal or ICS in the prior 5 yrs were included. In this way, it was hoped that most patients with new-onset COPD would be included and that subjects with prior asthma would be excluded. Subjects were also required to have been registered in the health plan for at least 5 yrs, in an attempt to exclude patients who had had an AMI in the 5 yrs prior to cohort entry. Subjects were followed until the date of first AMI, December 31, 1999, or the end of coverage (including emigration from the province or death), whichever came first.

Outcome

The outcome of interest was the first, fatal or nonfatal, AMI. Cases were identified using discharge diagnoses from the hospital separation database and underlying causes of death from the vital statistics information [18]. The date of first admission for AMI or date of death defined the index date. The recording of AMI in the hospital separation database has been previously studied. Compared to medical charts, diagnostic agreement in the hospital separation database was as high as 97% [17].

Study design

A nested case-control analysis was used within the cohort. This allows one to concentrate attention on exposure to medications in the time period directly leading up to the event of interest, AMI. Cases and all available controls were matched on age ($\pm$1 yr), as well as on the date of cohort entry ($\pm$6 months), in order to control for trends over time. Controls had to be at risk at the time of the AMI (index date) of the case to which they were matched; that is, controls had to be alive, resident in Saskatchewan, and free of the outcome (AMI).

Exposure

All ICS prescriptions identified from the drug prescription database were converted into beclomethasone-equivalent doses [19]. Subjects were considered currently exposed to ICS if they had been dispensed a canister of high-dose beclomethasone or budesonide within 60 days before the index date or a canister of low-dose beclomethasone or budesonide, or other types of ICS, within 30 days before the index date. When more than one canister was dispensed on the same day, the canisters were considered to have been used in successive time periods. Since dosage is not provided in the database, duration of each prescription was estimated based on clinical recommendations and on quantity dispensed. An average daily dose of ICS was calculated by dividing the total mg dispensed in the last 12 months by 365 or by the duration of follow-up in days when the latter was shorter than 1 yr. The average daily dose was then divided into three categories $<$50 μg, 50–200 μg and $>$200 $\mu g \cdot day^{-1}$. For currently exposed subjects, the duration of continuous exposure was defined as the period when, on average, one canister was filled in every 2-month period and allowing a lag of 1/3 of the prescription duration for the prescription to be refilled. The duration from the end of the last prescription defined how recent use was. Since no information is available on drugs dispensed in hospital, patients were excluded when they had durations of hospitalisation $>$30 days within 3 months or $>$90 days within the 12 months prior to index date.

Covariates

The following AMI risk factors were adjusted for: sex, systemic hypertension, diabetes, hyperlipidaemia, cardiovascular disease, defined as present or absent according to either drugs dispensed in the 1-yr period before cohort entry (systemic hypertension, diabetes, hyperlipidaemia) or discharge diagnoses anytime before cohort entry (heart failure) or both (ischaemic heart disease).

Severity of the respiratory disease was controlled for by matching on age and duration of disease, and by adjusting for COPD exacerbations and co-medications as follows: number of prescriptions for inhaled β_2-agonists, xanthines or ipratropium in the prior 12 months, and total number of mg of oral corticosteroids in the prior 12 months (expressed in hydrocortisone-equivalent mg). The number of exacerbations of COPD during follow-up was defined as the number of hospitalisations with COPD as the primary discharge diagnosis and the number of times where, within a 7-day time-window, antibiotics and corticosteroids were simultaneously prescribed.

Statistical analysis

All analyses used techniques for matched data. As the number of controls per case varied in each risk set, descriptive statistics were weighted by the inverse of the number of controls in each matched set. This is equivalent to standardising the number of controls to one control per case. A multivariate conditional logistic regression model was used to calculate odds ratios, equivalent to rate ratios (RR) in the nested case-control analysis, and 95% confidence intervals. The reference category was the absence of ICS use in the 12-month period prior to index date. The model was adjusted for the confounders and covariates that were found to modify the effect. To adjust for severity of COPD, different models were tested. In the final model, assessment of severity was based on the number of prior exacerbations, number of canisters of bronchodilators or prescriptions of nebulised bronchodilators (categorised as 0, 1–12 or $>$12) in the prior 12 months, and the dose of oral corticosteroids dispensed in the prior 12 months. In order to

assess whether oral corticosteroids might be related to AMI in a nonlinear fashion, quadratic splines were included in the conditional logistic regression model. This method splits the covariate range into a few segments, and fits a linear and quadratic term for each of these. A restriction is also added to ensure that the estimated hazard ratios are continuous across segments.

RESULTS

A cohort of 5,648 subjects receiving a first treatment for COPD was defined. A total of 694 subjects, whose records suggested they had suffered an AMI prior to cohort entry, were excluded. Among the 392 cases of a first AMI occurring after cohort entry, six cases were excluded because they had been first registered in the health plan <5 yrs previously and 15 others because they had durations of hospitalisation >30 days within 3 months or >90 days within the 12 months prior to index date, and, therefore, information on use of ICS was not available for a significant proportion of time. The same selection procedure was applied to controls. Therefore, the results are based on 371 cases (256 nonfatal AMI and 115 fatal AMI) who were matched to 1,864 controls. The mean age of subjects included in the analysis was 77.7 yrs (range 57–98). COPD therapy and medical characteristics at cohort entry are described in table 1.

The RR presented in tables 2–4 are adjusted for sex, severity of COPD, hospitalisation in the last 3 months, hypertension, diabetes, ischaemic heart disease and heart failure. The adjustment for treated hyperlipidaemia, use of aspirin and other anti-inflammatory agents did not modify the association between ICS use and AMI; therefore, these variables were not included in the final model.

In the prior year, ICS had been dispensed to 42.3% of case subjects (n=157) and 45.7% of controls (n=864) (table 2). The current use of ICS was associated with a RR of 0.82 (0.57–1.16). The RR for AMI was <1 for average daily doses of ICS <500 μg and returned to baseline for the larger doses (table 3). The second stratum of average daily dose (50–200 μg) was associated with a significant reduction in the risk of AMI (RR 0.68 (0.47–0.99)). The dose-related effect of ICS is described in a continuous way in figure 1.

The duration of continuous corticosteroid use was not associated with the risk of AMI (table 4). However, among current users, the mean duration of medication use was longer in controls than in cases, but not significantly so (table 4). How recently they were used was not associated with AMI risk (data not shown).

TABLE 1 Characteristics of the study subjects

Characteristics	Cases	Controls#
Subjects n	371	1864
Mean age yrs	77.7±8.6	77.7±3.8
Males	243 (65.5)	949 (50.8)
Duration of follow-up yrs	2.5±2.2	2.6±1.0
Medical characteristics at cohort entry		
Diabetes	60 (16.2)	128 (7.0)
Systemic hypertension	244 (65.8)	940 (52.2)
Hyperlipidaemia	16 (4.3)	59 (3.4)
Ischaemic heart disease	155 (41.8)	332 (18.1)
Heart failure	104 (28.0)	252 (13.7)
COPD co-therapy¶		
Prescriptions for inhaled β-agonists	2.2±3.6	2.0±1.5
Prescriptions for inhaled ipratropium	1.5±3.1	1.3±1.4
Prescriptions for nebulised β-agonists	1.4±4.1	1.2±2.1
Prescriptions for theophylline	0.9±2.7	0.9±1.2
Daily dose of oral corticosteroids mg hydrocortisone	3.7±11.2	2.3±3.1
COPD exacerbations+ prior to index date		
0	248 (66.9)	1320 (71)
1–2	84 (22.6)	411 (21.8)
⩾3	39 (10.5)	133 (7.2)
Hospitalisation in the last 3 months days		
None	261 (70.4)	1683 (90.3)
<7	61 (16.4)	75 (4.1)
7–13	28 (7.6)	66 (3.6)
⩾14	21 (5.7)	40 (2.0)
Aspirin at low dose	38 (10.2)	116 (6.6)
Other nonsteroidal anti-inflammatory agents	91 (24.5)	411 (22.3)

Data are presented as mean±SD or n (%). COPD: chronic obstructive pulmonary disease. #: to account for the variable number of controls in each matched set, all means, SD and percentages were weighted by the inverse of the number of controls in each set; ¶: in the 12 months before index date; +: defined as the number of hospitalisations with COPD as the primary discharge diagnosis and the number of times where, within a 7-day time-window, antibiotics and corticosteroids were simultaneously prescribed.

DISCUSSION

This study found a protective effect of ICS on the risk of AMI for daily medication doses ranging 50–200 μg of beclomethasone or the equivalent. For higher doses of ICS the risk returned to baseline.

The beneficial effects of ICS on the risk of AMI may be explained by the anti-inflammatory effects of ICS. The anti-inflammatory actions of corticosteroids encompass a wide variety of effects that are now considered as central components in the occurrence of AMI. Acute modifications of the atherosclerotic plaque that involve enhanced inflammatory activity within the plaque [7] and, possibly, throughout the entire coronary arteries [20], precipitate AMI. Anti-inflammatory actions of corticosteroids involve the modification of the expression of a wide number of genes, in turn, inhibiting the synthesis of cytokines (interleukin (IL)-2, IL-6, tumour necrosis factor -α, interferon-γ), adhesion molecules (intercellular adhesion molecule 1, endothelial leukocyte adhesion molecule 1), enzymes (inducible nitric oxide synthase, cyclooxygenase, collagenase) and other proteins (granulocyte-macrophage colony-stimulating factor) involved in inflammation [21, 22] and implicated in the pathogenesis of acute coronary syndromes [8]. Furthermore, the anti-atherogenic properties of corticosteroids have been demonstrated in several animal studies [23–26]. The lack of benefit at higher doses might plausibly reflect counterbalancing adverse effects on other risk factors or the fact that patients with more severe disease, itself linked to cardiovascular morbidity, are dispensed higher doses. Recently, SIN *et al.* [27] were able to show a reduction in

TABLE 2 Matched crude and adjusted rate ratios (RR) for acute myocardial infarction (AMI) in relation to the use of inhaled corticosteroids during the 1-yr period before index date[#]

	Case	Controls[¶]	Crude RR	Adjusted RR[+]
Subjects n	371	1864		
Exposure in the last 12 months				
None	214 (57.7)	1000 (54.3)	1 (ref. group)	1 (ref. group)
Any use	157 (42.3)	864 (45.7)	0.86 (0.68–1.09)	0.83 (0.63–1.08)
Current exposure[#]	71 (19.1)	359 (18.7)	0.95 (0.70–1.28)	0.82 (0.57–1.16)
Past exposure[#]	86 (23.2)	505 (27.1)	0.80 (0.60–1.06)	0.83 (0.61–1.14)

Data are presented as n (%) or RR (95% confidence interval), unless otherwise stated. ref.: reference. [#]: the index date for case subjects and matched controls was the date of the case subject AMI; [¶]: to account for the variable number of controls in each matched set, all means, SD and percentages were weighted by the inverse of the number of controls in each set; [+]: adjusted for age and duration of chronic obstructive pulmonary disease (COPD; by study design), and for sex, number of COPD exacerbations, number of prescriptions of bronchodilators in the last 12 months (none, 1–12, >12), oral corticosteroid dose dispensed in the last 12 months, hospitalisation in the last 3 months, diabetes, systemic hypertension, ischaemic heart disease and heart failure.

TABLE 3 Matched crude and adjusted rate ratios (RR) for acute myocardial infarction in relation to the quantity of inhaled corticosteroids dispensed in the prior year

	Case	Controls[#]	Crude RR	Adjusted RR[¶]
Subjects n	371	1864		
No exposure in the last 12 months	214 (57.7)	1000 (54.3)	1 (ref. group)	1 (ref. group)
Average daily dose in the last 12 months beclomethasone-equivalent units				
⩽50 μg·day^{-1}	19 (5.1)	123 (6.3)	0.74 (0.44–1.24)	0.82 (0.48–1.42)
50–200 μg·day^{-1}	47 (12.7)	322 (17.6)	0.68 (0.48–0.97)	0.68 (0.47–0.99)
200–500 μg·day^{-1}	39 (10.5)	199 (10.6)	0.92 (0.63–1.34)	0.84 (0.55–1.29)
>500 μg·day^{-1}	52 (14.0)	220 (11.3)	1.15 (0.81–1.63)	1.07 (0.71–1.60)

Data are presented as n (%) or RR (95% confidence interval), unless otherwise stated. ref.: reference. [#]: to account for the variable number of controls in each matched set, all means, SD and percentages were weighted by the inverse of the number of controls in each set; [¶]: adjusted for age and duration of chronic obstructive pulmonary disease (COPD; by study design), and for sex, number of COPD exacerbations, number of prescriptions of bronchodilators in the last 12 months (none, 1–12, >12), oral corticosteroid dose dispensed in the last 12 months, hospitalisation in the last 3 months, diabetes, systemic hypertension, ischaemic heart disease and heart failure.

TABLE 4 Matched crude and adjusted rate ratios (RR) for acute myocardial infarction in relation to the duration of inhaled corticosteroid use

	Case	Controls[#]	Crude RR	Adjusted RR[¶]
Subjects n	371	1864		
No exposure in the last 12 months	214 (57.7)	1000 (54.3)	1 (ref. group)	1 (ref. group)
Currently exposed				
1–30 days	25 (6.7)	130 (6.8)	0.92 (0.58–1.45)	0.78 (0.47–1.30)
31–60 days	19 (5.1)	58 (3.1)	1.53 (0.88–2.65)	1.17 (0.64–2.16)
>61 days	27 (7.3)	171 (8.8)	0.77 (0.49–1.19)	0.70 (0.43–1.15)
Duration months	3.1±5.1	4.7±3.3	0.97 (0.93–1.01)[+]	

Data are presented as n (%), mean±SD or RR (95% confidence interval), unless otherwise stated. ref.: reference. [#]: to account for the variable number of controls in each matched set, all means, SD and percentages were weighted by the inverse of the number of controls in each set; [¶]: adjusted for age and duration of chronic obstructive pulmonary disease (COPD; by study design), and for sex, number of COPD exacerbations, number of prescriptions of bronchodilators in the last 12 months (none, 1–12, >12), oral corticosteroid dose dispensed in the last 12 months, hospitalisation in the last 3 months, diabetes, systemic hypertension, ischaemic heart disease, and heart failure; [+]: associated with an increase of 1 month of continuous exposure.

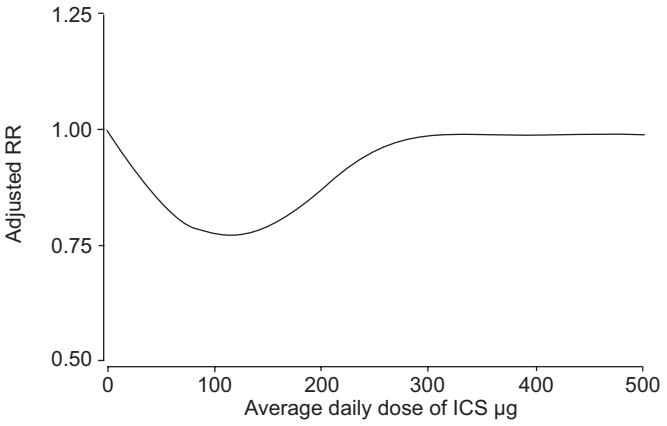

FIGURE 1. Fitted rate ratio (RR) for acute myocardial infarction as a function of the average daily dose of inhaled corticosteroids (ICS) in the 12 months prior to index date. Adjusted for age and duration of chronic obstructive pulmonary disease (COPD; by study design), and for the dose of oral corticosteroids, sex, number of prescriptions of bronchodilators in the last 12 months (none, 1–12, >12), number of COPD exacerbations, hospitalisation in the last 3 months, diabetes, systemic hypertension, ischaemic heart disease and heart failure.

C-reactive protein, itself a marker of increase in risk of acute coronary syndromes, with high doses of ICS over a period of several weeks.

Other explanations for the findings presented here are also possible. As discussed by SUISSA *et al.* [15], the observed effect of ICS on the risk of AMI may be due to a better control of the respiratory disease, either by a reduction of the number of acute exacerbations and the associated hypoxia, or by improving airflow limitation in a subgroup of steroid responders. Although ICS are of limited benefit in COPD, a meta-analysis of nine clinical trials showed a 30% reduction in the number of exacerbations in patients treated for >6 months with high-dose ICS [28]. The current analysis was adjusted for the number of exacerbations prior to the AMI, as well as for the quantity of bronchodilators and oral corticosteroids dispensed. Therefore, while residual confounding by severity of COPD may exist, the authors believe it is unlikely to explain the findings.

The present study has limitations that should be considered in interpreting the results. First, the doses on which the assessment of the effect of ICS were based are calculated from filled prescriptions. If subjects were taking less than the inferred dose dispensed, the beneficial effect of low doses of ICS on the risk of AMI may have been underestimated. Furthermore, the lack of a protective effect of ICS at higher doses argues against the possibility that the beneficial effect of low-dose ICS might reflect compliant behaviour with regular therapy of a condition, itself associated with better prognosis [29]. Secondly, there was the challenge of taking COPD severity into account. Controlling for age, duration of disease, frequency of COPD exacerbations and other dispensed therapy should, however, provide a good measure of COPD severity. Patients on ICS are likely to be more severe [1] and at higher risk for cardiovascular disease [30–32] than patients not receiving this treatment. Confounding by indication is therefore unlikely to explain the observed protective effect for doses ranging 50–200 µg of ICS. However, confounding by indication may mask a protective effect of larger doses of ICS because of possible residual confounding by severity of the lung disease. Further investigation of the dose of corticosteroids that would be of benefit is warranted.

A further limitation of the current study is the absence of information on smoking, an important risk factor for AMI not collected in administrative databases. To confound the association between ICS and AMI, current smoking would have to be associated with the use of ICS, even after adjusting for the number of exacerbations and concomitant respiratory medications.

In conclusion, the results presented here suggest that inhaled corticosteroids may be associated with a reduction in the risk of acute coronary events. This risk reduction was observed for doses of the medication ranging 50–200 $\mu g \cdot day^{-1}$ of beclomethasone or the equivalent. However, this therapeutic window may be dependent on the population and study setting. The mechanism of action is still unclear and it cannot be established whether the present results are due strictly to the dose or whether the route of administration may also play an important role. There is a need to further investigate the effect of inhaled corticosteroids on the risk of acute myocardial infarction since inhaled corticosteroids might provide some clinical benefits with few serious side-effects and at reasonable cost.

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