Cardiovascular morbidity and the use of inhaled bronchodilators

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Abstract: We used the Manitoba Health database to examine the relationship between use of inhaled respiratory drugs in people with chronic obstructive respiratory diseases and cardiovascular hospitalizations from 1996 through 2000. The drugs examined were beta agonists [BA], ipratropium bromide IB, and inhaled steroids (ICS). End points were first hospitalizations for supraventricular tachycardia, myocardial infarction, heart failure or stroke. A nested case control analysis was employed comparing people with and without cardiovascular events. Cases and controls were matched for gender and age, and conditional logistic regression was used in multivariate analysis considering other respiratory drugs, respiratory diagnosis and visit frequency, non-respiratory, non-cardiac comorbidities, and receipt of drugs for cardiovascular disease.

In univariate analyses, BA, IB and ICS were all associated with hospitalizations for cardiovascular disease, but in multivariate analyses ICS did not increase risk while both BA and IB did. There were interactions between respiratory and cardiac drugs receipt in that bronchodilator associated risks were higher in people not taking cardiac drugs; this was especially true for stroke. There were strong interactions with specific cardiac drugs; for example, both BA and IB substantially increased the risk of supraventricular tachycardia in patients not anti-arrhythmic agents, but not in the presence of such agents.

We conclude that bronchodilator therapy for chronic obstructive diseases is associated with increased cardiovascular risk, especially in patients without previous cardiovascular diagnoses, and that this is unlikely due to the severity of the respiratory disease, since risk was not increased with ICS.

Keywords: bronchodilator therapy, inhaled corticosteroids, nested case control study

Bronchodilators are widely used and effective drugs for the treatment of obstructive lung diseases. However, concerns have been raised about possible associations of these drugs with cardiovascular morbidity and mortality. Most reports have implicated inhaled beta agonists (BA), especially in patients with preexisting cardiac disease (Coughlin et al 1995; Au et al 2002, 2003, 2004; Salpeter et al 2004), but other studies have not found an association between these agents and cardiovascular outcomes (Suissa et al 1994, 1996, 2003). The other widely used bronchodilator, the anticholinergic ipratropium bromide (IB), has been less extensively studied in this regard. A large clinical trial involving IB in patients with mild COPD found a trend toward increased cardiovascular mortality and supraventricular tachycardias requiring hospitalization among participants assigned to IB as opposed to placebo (Anthonisen et al 2002). An association between IB and mortality had been noted previously in asthmatics (Guite et al 1999), but may have been confounded, since IB is more commonly used in COPD, and the two diseases are often confused. A retrospective cohort study also found IB use associated with increased mortality in both COPD and asthma (Ringbaek and Viskum 2003), but a large database study did not (Sin and Tu 2000).
It is well known that COPD patients have an increased risk of death from cardiovascular disease related to their smoking history and reduced lung function (Sin and Mann 2003; Sin et al 2005). There is also substantial prevalence of asymptomatic supraventricular and ventricular arrhythmias in people with severe COPD (Hudson et al 1973; Kleiger and Senior 1974). It is therefore conceivable that inhaled beta agonists or anti-cholinergics such as IB could cause arrhythmias and cardiovascular events in COPD patients. We have explored this possibility.

Methods

Data source
The Province of Manitoba provides universal health care insurance for all its residents (approximately 1.1 million). For research purposes, the Manitoba Population Health Research Repository integrates anonymous records of all inpatient and outpatient physician contacts, vital statistics (date and cause of death) and prescription records. In addition, it is linked via an anonymous identifier to the Population Registry, which indicates the duration of health insurance coverage for each permanent Manitoba resident, coverage ending with leaving the province or with death. Physicians are remunerated on the basis of claims for payment describing services provided and the diagnosis for which services were rendered. The Drug Programs Information Network (DPIN) database is created by provincial retail pharmacies entering prescriptions in real time in order to facilitate screening for inappropriate use, such as drug interactions, and co-payment for medication. The pharmaceutical database contains the individual anonymous identifier, as well as the information about the drug dispensed: the anatomical therapeutic chemical (ATC) code, drug identification number (DIN), date, quantity dispensed, and the number of days covered by the medication supplied (WHO 1995).

Subjects
We identified all people over 35 years of age who, between January 1, 1996 and December 31, 2000, had a physician contact for bronchitis (ICD-9 code 490) asthma (ICD-9 code 493) or COPD (ICD-9 codes 490, 491, 492, and 496) (WHO 1978). Subjects were permanent residents of the province on January 1, 1996 or at first physician contact after that date and were observed until leaving the province, death or December 31, 2000.

Variables
The outcome was the first hospitalization between January 1, 1996, and December 31, 2000, for selected cardiovascular events: supra-ventricular tachycardia (SVT) (ICD-9 427.0, 427.31, 427.32, 427.61), myocardial infarction (MI) (ICD-9 410), heart failure (HF) (ICD-9 428), and stroke (ICD-9 430-438).

Patients were classified according to sex, age, and respiratory diagnostic group: asthma, COPD, both asthma and COPD, and bronchitis. Patients in the first three groups could also have visits for bronchitis. Three groups of respiratory drugs were examined: inhaled beta agonists (BA), inhaled anti-cholinergics (IB), and inhaled corticosteroids (ICS). We recorded physician visits for respiratory diagnoses and for non-cardiac co-morbidities, and to assess cardiac co-morbidities we noted recipients of cardiac drugs. Non-cardiac co-morbidities were derived from physician claims for paralysis (ICD-9 342–344), diabetes (ICD-9 250), renal failure (ICD-9 403, 404, 582, 583, 585, 586, 588), liver disease (ICD-9 070, 456, 571, 572), peptic ulcer (ICD-9 531–534), malignancy (ICD-9 140–149, 200–203, 238, 273), collagen vascular disease (ICD-9 701, 710, 714, 720, 725) and dementia (ICD-9 290, 797). In assessing cardiac co-morbidities, cardiac medications were classified into 8 categories: anti-arrhythmics (excluding beta-blockers), nitrates, furosemide, beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors (ACEI), other anti-hypertensives, and cholesterol lowering agents. To assess co-morbidities, anti-arrhythmics were excluded from the analyses of SVT.

Design
We performed a nested case-control analyses with the first hospitalization for a specified cardiovascular event defining the case. The date of hospitalization of the case defined the index date. Each case was matched according to sex, age and duration of insurance coverage with up to ten control subjects that did not have that event prior to the index date. The control subjects were selected randomly if more than ten were available for a case. Respiratory drug exposure was analyzed according to receipt of one of the three types of drugs 60 days or 365 days prior to the event; it should be noted that those exposed within 365 days included those exposed within 60 days. Cardiac drug exposure was defined by receiving cardiac drugs within 365 days prior to the index date.

Analysis
Conditional logistic regression was used. Odds ratios (OR) and confidence intervals (95% CI) were calculated and results were considered statistically significant if p < 0.05. Analyses were conducted using SAS software, version 8.2 (SAS Institute, Inc., Cary, North Carolina). Univariate models assessed
the association of each drug group and exposure with each outcome. In multivariate models, we successively added other respiratory drugs, respiratory diagnostic group, number of physician visits for respiratory diagnoses, non-cardiac co-morbidities, and cardiac drugs. We also tested for interactions between cardiac drugs, taken as a whole, and respiratory drugs for each of the outcomes and looked for interactions with specific cardiac medications as follows: SVT (antiarrhythmics), MI (all except antiarrhythmics), HF (all except anticholesterol agents) and stroke (all cardiac drugs).

The Ethics Board of the University of Manitoba and the Health Information Privacy Committee of Manitoba Health approved the study.

Results
A total of 222,272 of Manitoba residents with a respiratory diagnosis were enumerated during 5 years ending on December 31, 2000. Characteristics of cases and controls are shown in Table 1 by cardio-vascular diagnosis at the time of the first hospitalization. The proportion of males was the highest (61.7%) among those hospitalized for myocardial infarction while those hospitalized for HF were the oldest (76.0 years). A relatively small proportion of cases received respiratory drugs during the year prior to the hospitalization, the highest being people with HF: about one third received BA. Use of BA and IB was more common in cases than controls. Also, ICS use was more common in cases, except for those with stroke. With respect to respiratory morbidity, cases and controls were well balanced for SVT, MI and stroke. For HF, a greater proportion had a history of COPD. As expected, use of cardiac drugs was substantially greater among cases than among controls. Non-cardiac co-morbidities were also more common in cases than in controls.

Tables 2–5 show univariate and multivariate associations between respiratory drugs and cardiovascular hospitalizations. The likelihood of a hospitalization for SVT, MI, and HF was significantly increased for those to whom BA, IB, or ICS were dispensed within 60 days or one year prior to the hospitalization. The association was weaker for those taking them.

We also found that IB use was associated with cardiovascular events to more or less the same extent as BA. This was not entirely unprecedented; a large clinical trial comparing IB with placebo in mild COPD noted increased cardiovascular morbidity and mortality of borderline significance in the group assigned IB, and a particularly suggestive increase in the incidence of SVT (Anthonisen et al 2002). This was consistent with the vagolytic nature of the drug if it was absorbed (Coleman et al 1975), and arrhythmias appear to be the most credible mechanism for IB to cause cardiovascular events. Other studies associating IB with excess mortality (Guite et al 1999; Rigbaek and Viskum 2003) suffered from potential confounders in that IB use was associated with
disease severity and/or the diagnosis of COPD as opposed to asthma. Using a very large database, Sin and Tu (2000) did not find an association between IB and mortality in COPD patients after adjustment for potential confounders.

The strength of any conclusions in regard to our data depends on the validity of our approach. Our database is inclusive and detailed. It included all residents of Manitoba: approximately 1.1 million people. We were able to enumerate

| Table 1 | Characteristics of cases (at first hospitalization) and controls |
|---------|---------------------------------------------------------------|
|         | SVT cases | Controls MI cases | Controls HF cases | Controls Stroke cases |
| Number of subjects | 2054 | 20501 | 3855 | 38490 | 5407 | 53929 | 4961 | 49487 |
| Gender | Males | | | | | | | |
| Age mean | 71.2 | | | | | | | |
| Respiratory Co-morbidity | | | | | | | | |
| Asthma | 10.1 | 10.9 | 9.6 | 11.0 | 7.1 | 9.1 | 8.0 | 10.0 |
| COPD | 27.1 | 26.3 | 29.5 | 25.6 | 41.7 | 28.9 | 31.5 | 27.9 |
| Asthma and COPD | 10.5 | 9.1 | 10.8 | 9.5 | 13.3 | 10.1 | 9.4 | 10.0 |
| Bronchitis | 52.3 | 53.7 | 50.1 | 53.9 | 37.9 | 52.1 | 51.1 | 52.2 |
| Any Non-cardiac Comorbidity | 39.5 | 34.0 | 44.4 | 32.9 | 51.7 | 35.8 | 46.2 | 34.9 |

| Drug dispensed within | | | | | | | | |
| IB 60 Days | 7.8 | 4.8 | 6.6 | 4.7 | 14.9 | 5.4 | 5.6 | 5.0 |
| I Year | 11.2 | 7.6 | 10.3 | 7.5 | 20.4 | 8.4 | 10.1 | 7.9 |
| BA 60 Days | 13.2 | 9.3 | 13.1 | 9.4 | 24.4 | 10.1 | 10.5 | 9.8 |
| I Year | 22.4 | 17.2 | 21.1 | 16.8 | 34.3 | 17.6 | 19.3 | 17.4 |
| ICS 60 Days | 7.2 | 6.4 | 7.9 | 6.2 | 12.0 | 6.9 | 6.1 | 6.7 |
| I Year | 13.5 | 11.3 | 14.0 | 11.6 | 18.7 | 12.0 | 11.6 | 11.7 |

| Cardiac Drugs | | | | | | | | |
| Antiarrhythmics | 36.8 | 9.2 | 11.8 | 7.9 | 34.6 | 9.8 | 16.8 | 9.6 |
| Nitrates | 31.0 | 16.1 | 30.1 | 13.7 | 40.7 | 16.6 | 25.0 | 16.4 |
| Antihypertensives | 37.5 | 27.6 | 32.4 | 25.7 | 42.0 | 28.8 | 37.8 | 28.1 |
| Furosemide | 33.9 | 17.3 | 23.8 | 14.5 | 65.0 | 18.8 | 27.8 | 18.2 |
| Betablockers | 29.4 | 14.1 | 20.1 | 12.8 | 20.7 | 13.8 | 20.4 | 13.8 |
| Calcium Channel Blockers | 16.5 | 7.6 | 12.4 | 6.6 | 15.2 | 7.7 | 11.3 | 7.4 |
| ACEI | 37.1 | 21.9 | 30.2 | 20.5 | 52.4 | 21.6 | 34.9 | 21.9 |
| Anticholesterol | 13.0 | 10.5 | 15.1 | 10.2 | 12.1 | 9.2 | 13.8 | 9.4 |
| Any | 81.2 | 55.3 | 67.4 | 51.6 | 88.9 | 58.6 | 73.2 | 56.7 |

| Table 2 | Odds ratios for the first hospitalization due to SVT |
|---------|-----------------------------------------------|
| Univariate | Multivariate |
| All Yes | Plus other | Plus cardiac | Interaction | No cardiac | Cardiac |
| All respiratory drugs | respiratory comorbidity | drugs | cardiac drugs p-value | drugs | drugs |
| IB 60 Days | 1.68 | 1.40 | 1.20, 1.86 | 1.38 | 0.011 | 2.38 | 1.24 |
| | 1.41, 2.00 | 1.19, 1.84 | 1.20, 1.86 | 1.20, 1.85 | 1.10, 1.72 | 1.51, 3.74 | 0.99, 1.55 |
| IB 1 Year | 1.48 | 1.40 | 1.17, 1.67 | 1.16, 1.69 | 1.37 | 0.05 | <0.05 |
| | 1.29, 1.70 | 1.17, 1.67 | 1.16, 1.69 | 1.14, 1.64 | 1.09, 1.57 | 1.51, 3.74 | 0.99, 1.55 |
| CS 60 Days | 1.13 | 0.79 | 0.64, 0.98 | 0.64, 0.98 | 0.80 | 0.05 | >0.05 |
| | 0.95, 1.35 | 0.79 | 0.64, 0.98 | 0.65, 0.99 | 0.64, 0.99 | 0.65, 0.99 | 0.64, 0.99 |
| I Year IB | 1.53 | 1.33 | 1.36 | 1.36 | 1.27 | 0.046 | 1.80 | 1.17 |
| | 1.32, 1.77 | 1.12, 1.59 | 1.13, 1.63 | 1.13, 1.63 | 1.06, 1.53 | 1.22, 2.65 | 0.97, 1.41 |
| BA 1 Year | 1.40 | 1.32 | 1.35 | 1.16, 1.57 | 1.14, 1.54 | 0.05 | >0.05 |
| | 1.25, 1.56 | 1.14, 1.53 | 1.16, 1.57 | 1.14, 1.54 | 1.07, 1.46 | 1.22, 2.65 | 0.97, 1.41 |
| CS 1.23 | 0.93 | 0.96 | 0.80, 1.14 | 0.80, 1.14 | 0.78, 1.11 | 0.78, 1.11 | 0.78, 1.11 |
| 1.07, 1.40 | 0.78, 1.09 | 0.80, 1.14 | 0.80, 1.14 | 0.78, 1.11 | 0.78, 1.11 | 0.78, 1.11 | 0.78, 1.11 |
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Table 3 Odds ratios for first hospitalization due to myocardial infarction

|                | Univariate |           |           | Multivariate |           |           | Interaction |
|----------------|------------|-----------|-----------|--------------|-----------|-----------|-------------|
|                | All respiratory drugs | Plus respiratory comorbidity |          | Plus other comorbidity | Plus cardiac drugs |          | p-value     |
|                |            |           |           |              |           |           |             |
| 60 Days        |            |           |           |              |           |           |             |
| IB             | 1.42       | 1.13      | 1.05      | 1.04         | 1.00      | >0.05     |             |
|                | 1.24, 1.63 | 0.96, 1.33| 0.89, 1.23| 0.88, 1.23   | 0.85, 1.18| >0.05     |             |
| BA             | 1.46       | 1.39      | 1.35      | 1.33         | 1.31      | >0.05     |             |
|                | 1.32, 1.61 | 1.22, 1.59| 1.18, 1.55| 1.16, 1.53   | 1.15, 1.51| >0.05     |             |
| CS             | 1.30       | 1.01      | 1.01      | 1.04         | 0.99      | >0.05     |             |
|                | 1.15, 1.48 | 0.87, 1.17| 0.87, 1.18| 0.89, 1.22   | 0.85, 1.16| >0.05     |             |
| 1 year         |            |           |           |              |           |           |             |
| IB             | 1.40       | 1.22      | 1.13      | 1.11         | 1.07      | >0.05     |             |
|                | 1.25, 1.57 | 1.07, 1.39| 0.98, 1.29| 0.97, 1.28   | 0.93, 1.23| >0.05     |             |
| BA             | 1.33       | 1.24      | 1.22      | 1.18         | 1.15      | >0.05     |             |
|                | 1.22, 1.44 | 1.11, 1.39| 1.08, 1.36| 1.05, 1.32   | 1.02, 1.29| >0.05     |             |
| CS             | 1.24       | 1.00      | 1.02      | 1.04         | 1.01      | >0.05     |             |
|                | 1.13, 1.37 | 0.89, 1.13| 0.89, 1.16| 0.91, 1.18   | 0.89, 1.15| >0.05     |             |

Table 4 Odds ratios for first hospitalization due to heart failure

|                | Univariate |           |           | Multivariate |           |           | Interaction |
|----------------|------------|-----------|-----------|--------------|-----------|-----------|-------------|
|                | All respiratory drugs | Plus respiratory comorbidity |          | Plus other comorbidity | Plus cardiac drugs |          | p-value     |
|                |            |           |           |              |           |           |             |
| 60 Days        |            |           |           |              |           |           |             |
| IB             | 3.07       | 1.80      | 1.59      | 1.59         | 1.47      | >0.05     |             |
|                | 2.82, 3.34 | 1.62, 2.00| 1.43, 1.77| 1.62, 1.78   | 1.31, 1.64| >0.05     |             |
| BA             | 2.88       | 2.45      | 2.25      | 2.21         | 1.99      | >0.05     |             |
|                | 2.69, 3.08 | 2.23, 2.68| 2.04, 2.47| 2.00, 2.43   | 1.81, 2.20| >0.05     |             |
| CS             | 1.84       | 0.82      | 0.83      | 0.87         | 0.85      | >0.05     |             |
|                | 1.69, 2.02 | 0.73, 0.91| 0.74, 0.92| 0.78, 0.97   | 0.76, 0.95| >0.05     |             |
| 1 year         |            |           |           |              |           |           |             |
| IB             | 2.80       | 1.90      | 1.69      | 1.68         | 1.55      | >0.05     |             |
|                | 2.60, 3.01 | 1.73, 2.08| 1.54, 1.86| 1.53, 1.85   | 1.41, 1.71| >0.05     |             |
| BA             | 2.45       | 2.15      | 2.03      | 1.96         | 1.74      | >0.05     |             |
|                | 2.31, 2.61 | 1.98, 2.33| 1.86, 2.21| 1.79, 2.13   | 1.60, 1.91| >0.05     |             |
| CS             | 1.69       | 0.78      | 0.82      | 0.84         | 0.82      | >0.05     |             |
|                | 1.57, 1.82 | 0.71, 0.86| 0.74, 0.90| 0.76, 0.93   | 0.75, 0.91| >0.05     |             |

claims for hospitalization, physician visits and all respiratory medications received by each subject with bronchitis, COPD or asthma. We attempted to control for disease severity and for cardiac and non-cardiac co-morbidities. As with all database studies, this had several important weaknesses. We cannot be certain of the accuracy of the diagnoses we were concerned with, though the accuracy of diagnosis of ischemic heart disease and COPD has been reported from a similar database (Curkendall et al 2006); agreement between databases and survey results is at best “moderate” in chronic diseases such as asthma (Huzel et al 2002). In the absence of laboratory data, we used proxies such as other drugs and physician visits to assess severity. We equated drug use with drug dispensing, and did not know whether patients actually used the medications that they received, though drug effects were most prominent in the 60 days after drug prescriptions, when it was reasonable to assume that the drugs were actually used. Although we adjusted for co-morbidities, such adjustments are approximations. We limited our analyses to first hospitalization for a cardiovascular diagnosis, thereby avoiding the weakness of pharmacy-derived drug databases do not enumerate drugs administered to hospitalized patients.

An alternative explanation for our results would be that bronchodilator use reflected severity of obstructive lung disease in a way that was not captured by our other measurements such as physician visits. There is excellent evidence...
Table 5 Odds ratios for first hospitalization due to stroke

|                | Univariate |                      | Multivariate | Interaction with cardiac drugs | No cardiac drugs | Cardiac drugs |
|----------------|------------|----------------------|--------------|-------------------------------|-----------------|--------------|
|                |            |                      |              |                               |                 |              |
|                | All         | Plus respiratory comorbidity | Plus other comorbidity | Plus cardiac drugs | p-value |                |               |
|                | respiratory drugs |                      |              |                               |                 |              |
| 60 Days        | IB          | 1.18                 | 1.09         | 1.10                          | 1.04           | <0.001       |
|                |             | 1.04, 1.33           | 0.93, 1.27   | 0.94, 1.28                    | 0.90, 1.22     | 1.05, 2.03   |
|                | BA          | 1.08                 | 1.05         | 1.05                          | 1.01           | <0.001       |
|                |             | 0.98, 1.19           | 0.92, 1.19   | 0.92, 1.19                    | 0.90, 1.15     | 1.05, 1.67   |
|                | CS          | 0.90                 | 0.78         | 0.80                          | 0.78           | >0.05        |
|                |             | 0.80, 1.02           | 0.68, 0.91   | 0.69, 0.92                    | 0.67, 0.90     |              |
| 1 year         | IB          | 1.30                 | 1.20         | 1.18                          | 1.13           | <0.001       |
|                |             | 1.18, 1.44           | 1.07, 1.36   | 1.05, 1.34                    | 1.00, 1.27     | 1.11, 1.87   |
|                | BA          | 1.13                 | 1.08         | 1.06                          | 1.01           | <0.001       |
|                |             | 1.05, 1.22           | 0.97, 1.19   | 0.96, 1.17                    | 0.92, 1.12     | 1.09, 1.57   |
|                | CS          | 0.99                 | 0.84         | 0.85                          | 0.83           | >0.05        |
|                |             | 0.90, 1.08           | 0.75, 0.93   | 0.76, 0.96                    | 0.74, 0.94     |              |

Table 6 Significant interactions between respiratory drugs and cardiac drug classes associated with causes of hospitalization*

| Cardiac drugs | Respiratory drugs | 60 Days | 365 Days |          |          |          |
|---------------|------------------|---------|----------|----------|----------|----------|
|               |                  | Off     | On       | p value  | Off      | On       | p value  |
| SVT           | IB and Antiarrhythmics | 1.76   | 0.72     | <0.0001  | 1.53     | 0.72     | <0.0001  |
|               |                  | 1.36, 2.27 | 0.52, 0.99 |          | 1.24, 1.89 | 0.55, 0.94 |          |
|               | BA and Antiarrhythmics | 1.32   | 0.77     | 0.0004   | 1.31     | 0.8      | 0.0001   |
|               |                  | 1.09, 1.61 | 0.60, 1.00 |          | 1.12, 1.52 | 0.65, 0.99 |          |
| Myocardial infarction | BA and Nitrates | 1.26   | 1.00     | 0.012    | 1.26     | 1.00     | 0.012    |
|               |                  | 1.13, 1.41 | 0.86, 1.17 |          | 1.13, 1.41 | 0.86, 1.17 |          |
| Heart failure | IB and Furosemide | 1.75   | 1.18     | 0.0002   | 1.73     | 1.26     | 0.0005   |
|               |                  | 1.45, 2.10 | 1.04, 1.34 |          | 1.48, 2.03 | 1.13, 1.40 |          |
|               | BA and Furosemide | 2.22   | 1.45     | <0.0001  | 1.68     | 1.28     | 0.0002   |
|               |                  | 1.94, 2.54 | 1.30, 1.61 |          | 1.50, 1.89 | 1.17, 1.41 |          |
| Stroke        | BA and ACEI      | 2.17   | 1.87     | 0.0417   |          |          |          |
|               |                  | 1.94, 2.43 | 1.66, 2.10 |          |          |          |          |
|               | IB and ACEI      | 1.26   | 0.88     | 0.006    | 1.33     | 1.01     | 0.01     |
|               |                  | 1.05, 1.50 | 0.70, 1.09 |          | 1.15, 1.54 | 0.86, 1.20 |          |
|               | BA and Antihypertensives | 1.06   | 0.84     | 0.018    | 1.06     | 0.89     | 0.03     |
|               |                  | 0.93, 1.21 | 0.71, 0.99 |          | 0.95, 1.17 | 0.78, 1.01 |          |

*Shown are odds ratios relating bronchodilators (IB or BA) to hospitalization for cardiovascular disease when patients were using (On) and not using (Off) groups of cardiac drugs.
the finding that there were significant interactive effects between bronchodilators and cardiac drugs taken as a whole (Table 3); in all cases cardiac drugs decreased the likelihood of cardiovascular events associated with bronchodilators, especially IB. The example of stroke was especially striking: on the whole bronchodilators did not increase stroke risk after adjustment for confounders, but risk was apparently dependent upon precognition of cardiovascular disease, since it was increased in those on bronchodilators who were not taking cardiac drugs. Specific drug interactions supported this interpretation (Table 6); in each case the receipt of specific cardiac drugs decreased the likelihood of hospitalizations associated with bronchodilator. A particularly notable example of this kind of drug interaction was the fact that bronchodilators did not increase the risk of arrhythmia in the presence of anti-arrhythmic agents. Bronchodilators apparently impose a larger relative risk in people with unrecognized cardiovascular disease than in people with known disorders.

As noted above, ICS were not associated with cardiovascular events. Indeed, they appeared to be protective, an effect that was occasionally significant. We have previously shown in a similar cohort that ICS were associated with reduced cardiovascular mortality as compared to patients taking bronchodilators in the absence of ICS (Macie et al 2006). It is possible that the beneficial effect of ICS is dependent upon reduction of cardiovascular events associated with bronchodilator therapy, since ICS are seldom used in the absence of bronchodilators.

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