

# Risk of non-fatal cardiac failure and ischaemic heart disease with long acting $\beta_2$ agonists

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## Abstract

**Background**—The long term safety of  $\beta$  agonists, particularly in patients with heart disease, has not been fully established.

**Methods**—This study accessed the results of three cohort studies involving: 12 294 patients receiving at least one prescription for nedocromil between November 1986 and September 1988; 15 407 patients prescribed salmeterol between December 1990 and May 1991; and 8098 patients prescribed bambuterol between February 1993 and December 1995. Details of all dispensed prescriptions for these drugs prescribed by general practitioners in England soon after their launch were provided in confidence by the Prescription Pricing Authority. Questionnaires were sent to the prescriber asking for details of events occurring after the first prescription (prescription event monitoring). Rates and relative risks of non-fatal cardiac failure and ischaemic heart disease were calculated, comparing bambuterol and salmeterol with the reference drug nedocromil.

**Results**—The age and sex adjusted relative risk of non-fatal cardiac failure associated with bambuterol was 3.41 (95% confidence limits (CL) 1.99 to 5.86) when compared with nedocromil. When salmeterol was compared with nedocromil the adjusted relative risk of non-fatal cardiac failure was 1.10 (95% CL 0.63 to 1.91). The adjusted relative risk of non-fatal ischaemic heart disease was 1.23 (95% CL 0.73 to 2.08) and 1.07 (95% CL 0.69 to 1.66) for bambuterol and salmeterol, compared with nedocromil, respectively. However, in the first month of exposure the adjusted relative risk of non-fatal ischaemic heart disease was 3.95 (95% CL 1.38 to 11.31) when bambuterol was compared with nedocromil.

**Conclusions**—Caution should be exercised when prescribing long acting oral  $\beta$  agonists to patients at risk of cardiac failure. More definitive evidence would come from prospective randomised trials.

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relatively  $\beta_2$  selective,<sup>3,4</sup> include tachycardia, prolonged Q-T interval, and raised blood pressure.<sup>4-6</sup> Oral  $\beta_2$  agonists have been associated with cardiac arrhythmia in otherwise healthy asthmatic patients.<sup>7</sup> Myocardial ischaemia has been reported in women receiving the intravenous  $\beta_2$  agonist, ritodrine, for the treatment of premature uterine contractions.<sup>8</sup> A recent case control study found an increased rate of cardiovascular death in users of oral and nebulised  $\beta$  agonists, but not in users of inhaled  $\beta$  agonists, after controlling for age and prior use of cardiac drugs.<sup>2</sup> Another study suggested an association between use of oral  $\beta$  agonists, and  $\beta$  agonists taken by inhaler or by nebulisation, and idiopathic dilated cardiomyopathy.<sup>1</sup>

In general, however, comparative data on the profiles of adverse cardiac effects with different  $\beta_2$  agonists, when used in general medical practice, are limited. To examine further the relation between cardiovascular events and clinical use of  $\beta$  agonists, we accessed the results of three cohort studies of antiasthma treatment performed by the Drug Safety Research Unit, Southampton. These studies, conducted by prescription event monitoring, linked the prescription of a drug in general practice to events experienced by the patient after that drug was dispensed.<sup>9-10</sup> These data allow hypotheses to be generated about possible adverse drug effects, which can then be tested in conventional case control or other studies. In this paper we report a hypothesis generating study in which we compared rates of adverse cardiovascular events reported in prescription event monitoring studies of salmeterol (an inhaled  $\beta_2$  agonist), bambuterol (an oral  $\beta_2$  agonist), and nedocromil (a mast cell stabiliser). A report on the salmeterol cohort has been published.<sup>11</sup>

## Methods

The methodology of prescription event monitoring has been described.<sup>9-11</sup> Details of all dispensed prescriptions for selected newly marketed drugs, prescribed by general practitioners in England soon after launch, are provided in confidence by the Prescription Pricing Authority. Questionnaires, known as "green forms", are then sent to the prescriber asking for details and dates of events occurring after the drugs were prescribed. The definition of an event provided on the green forms is "any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected adverse drug reaction, or any other complaint that was considered of sufficient importance to enter in the

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The long term safety of  $\beta$  agonists, particularly in patients with heart disease, has not been fully established.<sup>1-3</sup> The cardiac effects of  $\beta$  agonists, including newer agents that are

Table 1 Characteristics of the cohorts

	Nedocromil	Salmeterol	Bambuterol
Dates of studies	November 1986 to September 1988	December 1990 to May 1991	February 1993 to December 1995
Total number of green forms posted	20644	28019	18013
Total number of green forms returned with usable data* (% response rate)	12294 (59.6)	15407 (55.0)	8098 (45.0)
Overall number of patient-months of exposure	77674	172753	32926
Men (% of cohort)	6340 (51.6)	7844 (50.9)	3631 (44.8)
Women (% of cohort)	5768 (46.9)	7445 (48.3)	4400 (54.3)
Sex not known	186 (1.5)	118 (0.8)	67 (0.8)
Median age (years) (interquartile range)	46 (24–62)	55 (34–67)	60 (38–72)
Recorded indication for study drug (%)			
Asthma/wheeze	7487 (60.9)	10820 (70.2)	4637 (57.3)
Chronic obstructive airways disease	1247 (10.1)	1816 (11.8)	1209 (14.9)
Others†	1336 (10.9)	424 (2.8)	1040 (12.8)
Unknown	2224 (18.1)	2346 (15.2)	1212 (15.0)

\*Final cohort; †others includes dyspnoea, bronchitis, cough, chest infection, emphysema, and bronchiectasis.

Table 2 Incidence densities of cardiac failure and ischaemic heart disease during treatment with three antiasthma drugs studied by prescription event monitoring

Event and drug	Sex (M:F)	Mean (SD) age	ID <sub>1</sub>	ID <sub>2</sub>	ID <sub>1</sub> – ID <sub>2</sub> (99% CI)
<b>Cardiac failure</b>					
Bambuterol	0.8:1	58.5 (18.6)	4.9	2.8	2.2 (–0.4 to 4.8)
Salmeterol	1.1:1.0	54.3 (19.5)	0.9	0.6	0.3 (–0.4 to 1.0)
Nedocromil	1.1:1.0	48.2 (20.5)	0.6	0.4	0.2 (–0.5 to 0.9)
<b>Ischaemic heart disease</b>					
Bambuterol	0.8:1.0	58.5 (18.6)	2.4	1.1	1.3 (–0.5 to 3.1)
Salmeterol	1.1:1.0	54.3 (19.5)	1.0	1.1	–0.1 (–0.9 to 0.7)
Nedocromil	1.1:1.0	48.2 (20.5)	0.6	1.0	–0.4 (–1.2 to 0.4)

ID<sub>1</sub>, incidence density (number of events per 1000 patient-months of exposure) for each event during the first month of treatment.

ID<sub>2</sub>, incidence density (number of events per 1000 patient-months of exposure) for each event during treatment months 2–6.

patient's notes". The doctor is not required to give an opinion on whether or not events were drug related. Other information obtained includes the date of birth of the patient, the indication for the study drug, and the dates of starting and stopping treatment with the study drug.

In the present analysis we studied patients receiving at least one prescription for nedocromil between November 1986 and September 1988, salmeterol between December 1990 and May 1991, and bambuterol between February 1993 and December 1995. The median (interquartile range) follow up time in these studies was 457 (420 to 515) days for nedocromil, 511 (431 to 656) days for salmeterol, and 288 (238 to 370) days for bambuterol.

#### STATISTICAL ANALYSIS

The data from the green forms were entered into a computer using the Drug Safety Research Unit dictionary which is arranged in system organ classes. For each study drug, event rates (number of events per 1000 patient months of exposure) were calculated. These rates are termed incidence densities (IDs) and their calculation and justification has been described.<sup>9</sup> As part of the hypothesis generating studies performed at the Drug Safety Research Unit, incidence densities are routinely calculated for the first month (month 1) of drug exposure (ID<sub>1</sub>), for the second to the sixth month (months 2 to 6) of exposure (ID<sub>2</sub>), and for all treatment months of exposure (ID<sub>A</sub>). The arithmetic difference between ID<sub>1</sub> and ID<sub>2</sub>

is routinely calculated. Examination of these data showed that rates of ischaemic heart disease and cardiac failure differed in the three cohorts. We were prompted, therefore, to examine more closely these rates in the three cohorts. For non-fatal ischaemic heart disease and non-fatal cardiac failure, we calculated crude and adjusted relative risks comparing bambuterol and salmeterol with the reference drug nedocromil. We examined the effects of age, sex, recorded indication, and season of starting the drug on the relative risk estimates using weighted Mantel-Haenszel estimates and Poisson regression analysis where appropriate. As the follow up time differed between the three cohorts, we calculated relative risks for the first six months of exposure for all three drugs. We also calculated age and time specific rates (per 1000 patient months of exposure), and age and time specific adjusted relative risks. Calculation of rates, relative risks and 95% confidence limits were performed using Stata Statistical Software Release 5.0.<sup>12</sup>

#### Results

The background characteristics of the three cohorts are given in table 1. The final number of patients for whom event data were obtained for nedocromil was 12 294, for salmeterol was 15 407, and for bambuterol was 8098. The median age (interquartile range) of patients prescribed nedocromil was 46 (24 to 62) years, salmeterol was 55 (34 to 67) years and bambuterol was 60 (38 to 72) years. The sex distribution was similar in the three cohorts. The proportion of patients with a diagnosis of asthma/wheeze and chronic obstructive pulmonary disease was: 60.9% and 10.1%, respectively, for nedocromil; 70.2% and 11.8%, respectively, for salmeterol; and 57.3% and 14.9%, respectively, for bambuterol.

Table 2 presents ID<sub>1</sub>, ID<sub>2</sub>, and the arithmetic difference between ID<sub>1</sub> and ID<sub>2</sub> for the events cardiac failure and ischaemic heart disease. ID<sub>1</sub>, ID<sub>2</sub>, and the arithmetic difference between ID<sub>1</sub> and ID<sub>2</sub> were higher in the bambuterol cohorts than in the salmeterol and nedocromil cohorts. These findings led us to examine the effects of age, sex, indication, season of starting the drug, and time since starting the drug, on the rates of these events in the three cohorts.

Table 3 presents the numbers of patients with non-fatal cardiac failure and ischaemic heart disease in the cohorts during the first six months of exposure, the crude incidence rate estimates per 1000 patient months of exposure, and the adjusted relative risk estimates. The age and sex adjusted relative risk of non-fatal cardiac failure associated with bambuterol was 3.41 (95% confidence limits (CL) 1.99 to 5.86) when compared with nedocromil ( $p < 0.0001$ ). When salmeterol was compared with nedocromil the adjusted relative risk was 1.10 (95% CL 0.63 to 1.91;  $p = 0.7$ ). The adjusted relative risk of non-fatal ischaemic heart disease was 1.23 (95% CL 0.73 to 2.08;  $p = 0.4$ ) and 1.07 (95% CL 0.69 to 1.66;  $p = 0.8$ ) for bambuterol and salmeterol, respectively. Adjusting for indication and season of starting treatment had little effect on the age

Table 3 Results of cohort analysis on risk of non-fatal congestive cardiac failure and ischaemic heart disease with  $\beta_2$  agonists in the first six months of exposure

	Nedocromil*	Salmeterol	Bambuterol
<i>Non-fatal cardiac failure</i>			
Number of patients with a report of cardiac failure in first 6 months of exposure	18	45	64
Patient-months of exposure	38265.5	64350.4	20667.5
Crude overall incidence rate estimates per 1000 patient-months of exposure	0.47	0.70	3.10
Crude relative risk (95% CL)	1	1.49 (0.86 to 2.57)	6.58 (3.90 to 11.10)†
Relative risk adjusted for age and sex (95% CL)	1	1.10 (0.63 to 1.91)	3.41 (1.99 to 5.86)†
Relative risk adjusted for age, sex, indication and season of starting treatment (95% CL)	1	0.90 (0.50 to 1.60)	3.31 (1.91 to 5.71)†
<i>Non-fatal ischaemic heart disease</i>			
No. of patients with a report of ischaemic heart disease	29	66	26
Patient-months of exposure	38226.0	64308.1	20742.4
Crude overall incidence rate estimates per 1000 patient-months of exposure	0.76	1.03	1.25
Crude relative risk (95% CL)	1	1.35 (0.87 to 2.09)	1.65 (0.97 to 2.80)
Relative risk adjusted for age and sex (95% CL)	1	1.07 (0.69 to 1.66)	1.23 (0.73 to 2.08)
Relative risk adjusted for age, sex, indication, and season of starting treatment (95% CL)	1	0.94 (0.58 to 1.54)	1.31 (0.76 to 2.26)

\*Reference drug; †p<0.0001.

and sex adjusted relative risk estimates. The relative risk of non-fatal cardiac failure with bambuterol compared to salmeterol was 2.91 (95% CL 1.96 to 4.31; p<0.0001) after adjusting for age and sex.

We calculated age and time specific rates of non-fatal cardiac failure and ischaemic heart disease with bambuterol and salmeterol compared with nedocromil. The risk of non-fatal cardiac failure with bambuterol compared to nedocromil was 3.15 (95% CL 1.27 to 7.80) in the 71 to 80 year age group (p = 0.009). The risk of cardiac failure was also increased in the under 30 year age group, but the numbers were small and the confidence limits were too wide to draw valid conclusions. There were no differences in rates of cardiac failure when salmeterol was compared with nedocromil. However, when bambuterol was compared with salmeterol, the age specific relative risk of cardiac failure was 2.30 (95% CL 1.03 to 5.11; p = 0.04) between 61 and 70 years, 2.92 (95% CL 1.51 to 5.67; p = 0.001) between 71 and 80 years and 2.50 (95% CL 1.16 to 5.58; p = 0.02) after 81 years of age. There were no significant differences in age specific rates of non-fatal ischaemic heart disease when bambuterol and salmeterol were compared with nedocromil.

Table 4 Time specific relative risks of non-fatal ischaemic heart disease and cardiac failure

Month and event	Patients (n)	Unadjusted relative risks (95% CL)	Age and sex adjusted relative risks (95% CL)
<i>Cardiac failure</i>			
Month 1			
Nedocromil*	6	1	1
Salmeterol	10	1.23 (0.45 to 3.40)	0.81 (0.29 to 2.25)
Bambuterol	31	8.41 (3.51 to 20.15)§	4.41 (1.90 to 10.27)§
Months 2-6			
Nedocromil*	12	1	1
Salmeterol	35	1.67 (0.85 to 3.14)	1.25 (0.64 to 2.44)
Bambuterol	33	5.34 (2.76 to 10.33)§	2.67 (1.30 to 5.47)†
<i>Ischaemic heart disease</i>			
Month 1			
Nedocromil*	5	1	1
Salmeterol	12	1.78 (0.63 to 5.04)	1.32 (0.46 to 3.78)
Bambuterol	14	4.55 (1.64 to 12.63)‡	3.95 (1.38 to 11.31)†
Months 2-6			
Nedocromil*	24	1	1
Salmeterol	54	1.26 (0.78 to 2.03)	1.01 (0.62 to 1.63)
Bambuterol	12	0.96 (0.48 to 1.93)	0.67 (0.34 to 1.34)

\*Reference drug; †p<0.01; ‡p=0.001; §p<0.0001.

Table 4 shows the results of examining the risk of non-fatal cardiac failure in month 1 of treatment, and in months 2 to 6 of treatment. The unadjusted relative risk of cardiac failure with bambuterol in month 1 was 8.41 (95% CL 3.51 to 20.15; p<0.0001) compared with nedocromil. In months 2 to 6, the relative risk compared with nedocromil was 5.34 (95% CL 2.76 to 10.33; p<0.0001). After adjusting for age and sex, significant differences in the risk of cardiac failure remained between bambuterol and nedocromil in month 1 (4.41, 95% CL 1.90 to 10.27; p<0.0001) and months 2 to 6 (2.67, 95% CL 1.30 to 5.47; p<0.01). When the risk of cardiac failure with bambuterol was compared to salmeterol the adjusted relative risks were significant in month 1 (4.18, 95% CL 2.16 to 8.10; p<0.0001) and months 2 to 6 (2.16, 1.29 to 3.62; p = 0.003). The risk of ischaemic heart disease was increased for bambuterol compared with nedocromil during the first month of treatment only (4.55, 95% CL 1.64 to 12.63; p = 0.001). The increased risk remained after adjusting for age and sex (3.95, 95% CL 1.38 to 11.31; p = 0.006).

## Discussion

Prescription event monitoring studies are designed to generate hypotheses about possible adverse events associated with newly marketed drugs. The technique used at the Drug Safety Research Unit to generate hypotheses is to compute summary event rates (incidence densities) during different time periods from the date each patient starts treatment. These rates can be compared within and between drugs to look for differences. In this comparative study, we were prompted to examine rates of cardiac failure and ischaemic heart disease after an examination of the incidence densities for the three antiasthma drugs on the database. The study was therefore data driven ("hypothesis generating"), but we did not dredge the database for "significant" results.

We found that the risk of non-fatal cardiac failure with bambuterol, but not salmeterol, was increased when compared with nedocromil after adjusting for age, sex, indication, and season of starting treatment. When

age specific relative risks comparing bambuterol with nedocromil were calculated, a significant difference was found only in the 71 to 80 year old age group. However, when the risk of cardiac failure with bambuterol was compared with salmeterol, age specific relative risks were significantly increased in all age groups above 60 years. There were no differences in any age group when salmeterol was compared with nedocromil. The age and sex adjusted risk of cardiac failure with bambuterol was highest during the first month of exposure (4.41, 95% CL 1.90 to 10.27) and was also significantly increased in months 2 to 6 (2.67, 95% CL 1.30 to 5.47).

The adjusted relative risk of non-fatal ischaemic heart disease was not significantly increased when bambuterol or salmeterol were compared with nedocromil. However, there was an increased risk of non-fatal ischaemic heart disease when bambuterol was compared with nedocromil in the first month of exposure, which remained after adjusting for age and sex. The association with ischaemic heart disease was therefore weak and this result should be interpreted cautiously.

Our results are in line with a recent study that found an association between oral  $\beta$  agonists, but not inhaled  $\beta$  agonists, and cardiovascular death.<sup>2</sup> Oral  $\beta$  agonists provide a greater systemic dose than that achieved with metered dose inhalers at doses commonly prescribed.<sup>3-13</sup> The validity of this increase in risk is also supported by reports of tachycardia and prolonged Q-T interval occurring principally with nebulised or oral  $\beta$  agonists.<sup>14-15</sup> Angina and ventricular extrasystoles have been reported in elderly patients and those with known cardiac disease who have been exposed to nebulised  $\beta$  agonists.<sup>16</sup> Increased heart rate is a known indicator of poor outcome in heart failure.<sup>17</sup> Some  $\beta$  blockers have been shown to be beneficial in heart failure,<sup>18-21</sup> whereas drugs that increase heart rate may be harmful in patients with heart failure.<sup>22</sup> It is possible that it is the tachycardia associated with  $\beta$  agonists that explains the increased risk of cardiac failure with bambuterol seen in this study.

The results may be biased by exclusion of fatal events if patients in the nedocromil and salmeterol cohorts had a higher rate of deaths from cardiac failure or ischaemic heart disease. We did not include fatal events in this analysis because of concerns about the accuracy of certification of causes of death,<sup>23-24</sup> difficulties in coding multiple entries on death certificates,<sup>25</sup> because heart failure is often a terminal event and not the underlying cause of death,<sup>25</sup> and because we found that complete data on dates of drug exposure were uncertain in many patients who had died. We have looked at death rates using patient months of observation as the denominator, and using the World Health Organisation conventions for coding deaths adopted by the Office of Population Censuses and Surveys in 1984.<sup>25</sup> We found that the associations between bambuterol and fatal events were in the same direction as the associations described in this paper for non-fatal events.

This suggests that our results were not biased by exclusion of fatal events.

The older age of the bambuterol users may partially explain the differences seen. The analysis revealed that adjusting for age and sex had the effect of reducing the relative risk estimates considerably. However, this does not exclude some residual confounding. The relative risk estimates may be further confounded by other factors such as smoking, a history of cardiac disease, blood cholesterol, diabetes, and use of cardiac drugs. Confounding would occur if these factors were associated with both drug exposure and cardiac failure. We do not have comprehensive data on these variables to enable us to determine if they are potential confounding factors. In view of the recommended indications and cautions listed in the *British National Formulary* for salmeterol and bambuterol, it seems unlikely that these drugs were preferentially prescribed to patients with these risk factors.

Coronary heart disease is an important aetiological factor in the development of cardiac failure.<sup>26</sup> If bambuterol was prescribed preferentially to patients at high risk of cardiac failure, we would reasonably expect the bambuterol cohort to have a high risk of ischaemic heart disease as well. Consequently, we would expect to have found an association between bambuterol and ischaemic heart disease compared with salmeterol and nedocromil. However, there was no association between bambuterol and ischaemic heart disease, except in a subanalysis of the first treatment month. This suggests that the effect of confounding by risk factors for cardiac disease is limited and is unlikely to explain the magnitude of the association that we found.

There is potential for bias by the different indications for the study drugs. Although correcting for reported indication made little difference to the relative risks, it is possible that reported indication masked differences in the types of patients given these drugs, the severity of their disease, or both. We attempted to assess this by examining asthma death rates in the bambuterol and salmeterol cohorts. There were 12 deaths due to asthma after follow up in the bambuterol cohort. The crude asthma death rate was 19.1 per 10 000 years of observation (95% CL 9.9 to 33.4). There were 73 asthma deaths in the salmeterol cohort after follow up,<sup>10</sup> giving a crude death rate of 35.6 per 10 000 years of observation (95% CL 28.5 to 46.3). These results could have resulted from differences in indication, disease severity, asthma management, or drug effectiveness. If there were differences in indication or severity that we could not control for, this bias would have contributed to the association between bambuterol and cardiac failure that we found, if differences in indication or severity were associated with an increased risk of cardiac failure. It has been suggested that severe chronic pulmonary disease is associated with heart failure.<sup>27</sup> However, asthma death rates were higher in the salmeterol than the bambuterol cohort, arguing against the possibility that the bambuterol cohort may have had a



higher risk of heart failure because of more severe or poorly treated pulmonary disease.

The response rate for bambuterol was relatively low and it could be argued that doctors may have been more likely to respond in this cohort if an event had occurred. However, response bias is unlikely to have differentially affected reporting of cardiac failure, because cardiac failure is not a recognised side effect of one or other  $\beta$  agonist. The onset of cardiac failure is insidious and the patients may not necessarily have been incident cases, despite our surveys specifically requesting information on new events. It is possible that oral  $\beta$  agonists may worsen or "unmask" previously existing cardiac failure, rather than being cardiotoxic. This hypothesis may explain why the risk of cardiac failure was highest in the first month of exposure, but would not necessarily explain the significantly increased risk in months 2 to 6 of exposure.

The periods of observation for the three drugs were not concurrent. It is theoretically possible that adverse influences present during the bambuterol study period, and not during the nedocromil or salmeterol study periods, may have affected the results. We evaluated this by calculating cardiac failure rates during two prescription event monitoring studies of non-respiratory/non-cardiac drugs performed during the same time as bambuterol, and which had a similar age distribution (famciclovir and lansoprazole). The rates were 0.5 per 1000 patient months of observation (famciclovir) and 0.7 per 1000 patient months of exposure (lansoprazole). These rates are similar to the salmeterol and nedocromil results and suggest that there were no unsuspected adverse influences during the bambuterol study period.

The present study provides evidence that oral  $\beta$  agonists are associated with an increased risk of non-fatal cardiac failure, although the nature of the association is uncertain. For prescribing doctors, cardiac failure is likely to be difficult to diagnose as a drug induced event in individual patients. It is notable that there have been no spontaneous reports of cardiac failure or ischaemic heart disease with bambuterol reported to the Committee on Safety of Medicines to date (Committee on Safety of Medicines, personal communication 1997). Taken together with other studies, the present analysis suggests that doctors should exercise caution when prescribing oral  $\beta$  agonists to elderly patients at risk of cardiac failure, whatever the explanation for the associations. More definitive evidence would come from prospective randomised controlled trials.

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