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## Cardiovascular Effects of $\beta$ -Agonists in Patients With Asthma and COPD: A Meta-Analysis

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*Chest* 2004;125:2309-2321

DOI: 10.1378/chest.125.6.2309

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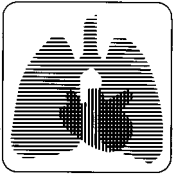
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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S



## special report

# Cardiovascular Effects of $\beta$ -Agonists in Patients With Asthma and COPD\*

## A Meta-Analysis

Shelley R. Salpeter, MD; Thomas M. Ormiston, MD; and  
Edwin E. Salpeter, PhD

**Background:**  $\beta$ -Adrenergic agonists exert physiologic effects that are the opposite of those of  $\beta$ -blockers.  $\beta$ -Blockers are known to reduce morbidity and mortality in patients with cardiac disease.  $\beta_2$ -Agonist use in patients with obstructive airway disease has been associated with an increased risk for myocardial infarction, congestive heart failure, cardiac arrest, and acute cardiac death.

**Objectives:** To assess the cardiovascular safety of  $\beta_2$ -agonist use in patients with obstructive airway disease, defined as asthma or COPD.

**Methods:** A meta-analysis of randomized placebo-controlled trials of  $\beta_2$ -agonist treatment in patients with obstructive airway disease was performed, to evaluate the short-term effect on heart rate and potassium concentrations, and the long-term effect on adverse cardiovascular events. Longer duration trials were included in the analysis if they reported at least one adverse event. Adverse events included sinus and ventricular tachycardia, syncope, atrial fibrillation, congestive heart failure, myocardial infarction, cardiac arrest, or sudden death.

**Results:** Thirteen single-dose trials and 20 longer duration trials were included in the study. A single dose of  $\beta_2$ -agonist increased the heart rate by 9.12 beats/min (95% confidence interval [CI], 5.32 to 12.92) and reduced the potassium concentration by 0.36 mmol/L (95% CI, 0.18 to 0.54), compared to placebo. For trials lasting from 3 days to 1 year,  $\beta_2$ -agonist treatment significantly increased the risk for a cardiovascular event (relative risk [RR], 2.54; 95% CI, 1.59 to 4.05) compared to placebo. The RR for sinus tachycardia alone was 3.06 (95% CI, 1.70 to 5.50), and for all other events it was 1.66 (95% CI, 0.76 to 3.6).

**Conclusion:**  $\beta_2$ -Agonist use in patients with obstructive airway disease increases the risk for adverse cardiovascular events. The initiation of treatment increases heart rate and reduces potassium concentrations compared to placebo. It could be through these mechanisms, and other effects of  $\beta$ -adrenergic stimulation, that  $\beta_2$ -agonists may precipitate ischemia, congestive heart failure, arrhythmias, and sudden death.  
(*CHEST* 2004; 125:2309–2321)

**Key words:** adrenergic  $\beta$ -agonists; adverse effects; asthma; cardiovascular; COPD

**Abbreviations:** CI = confidence interval; OR = odds ratio; RR = relative risk

The  $\beta$ -adrenergic system contains  $\beta_1$  and  $\beta_2$  receptors that are found in varying concentrations in the heart and lung, as well as in peripheral tissues throughout the body.<sup>1,2</sup>  $\beta_1$ -Adrenergic receptors and  $\beta_2$ -adrenergic receptors coexist in the heart, gener-

ally in a ratio of 3:1, respectively.<sup>1</sup>  $\beta_2$  Receptors are also present on adrenergic nerve terminals in the heart, where they facilitate norepinephrine release.<sup>1</sup> The stimulation of either receptor results in positive inotropic and chronotropic responses, cardiac myo-

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Manuscript received July 7, 2003; revision accepted November 21, 2003.

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cyte growth, and cardiac toxicity.<sup>1</sup>  $\beta_2$  Receptors are found predominately in bronchial and vascular smooth muscle, peripheral leukocytes, and adrenergic nerves.<sup>2</sup>  $\beta_2$ -Agonists, such as albuterol and salmeterol, are widely used as bronchodilators in the treatment of asthma and COPD.

The use of  $\beta$ -blockers has been shown to reduce morbidity and mortality in patients with ischemic heart disease, myocardial infarction, congestive heart failure, cardiac arrhythmias, and hypertension, as well as in the perioperative period.<sup>1,3-7</sup>  $\beta$ -Agonists exert physiologic effects that are the opposite of those of  $\beta$ -blockers and may be expected to have deleterious cardiovascular effects.<sup>8</sup> Doubts have gradually been emerging concerning the cardiovascular safety of  $\beta_2$ -agonist use, especially in patients who are at risk for heart disease.<sup>8,9</sup> Case-control studies<sup>10-16</sup> have demonstrated an association between  $\beta_2$ -agonist use and an increased risk for myocardial infarction, congestive heart failure, cardiac arrest, and acute cardiac death, with odds ratios (ORs) ranging from 1.3 to 3.4.

The objective of this analysis was to evaluate the cardiovascular effects of  $\beta_2$ -agonist use in patients with *obstructive airway disease*, which was defined as asthma or COPD. Data from randomized placebo-controlled trials were pooled in order to assess the short-term effect of  $\beta_2$ -agonist use on heart rate and potassium concentration, and the long-term effect on adverse cardiovascular events. The results of this meta-analysis also have been reported in a systematic review on the cardiovascular safety of  $\beta$ -agonist use.<sup>17</sup>

## MATERIALS AND METHODS

### Search Strategy

A comprehensive search of the EMBASE, MEDLINE, and CINAHL databases was performed to identify randomized placebo-controlled trials on  $\beta$ -agonist use in patients with obstructive airway disease, published between 1966 and June 2003. The search was performed using the terms *bronchodilator*, *sympathomimetic*, *adrenergic  $\beta$ -agonist*, *albuterol*, *salbutamol*, *bitolterol*, *isoetharine*, *metaproterenol*, *salmeterol*, *terbutaline*, *fenoterol*, *formoterol*, *procaterol*, *isoproterenol*, *reproterol*, *efomotorol*, or *bambuterol*, and *asthma\**, *bronchial hyperreactivity*, *respiratory sounds*, *wheeze\**, *respiratory hypersensitivity*, *obstructive lung disease*, *obstructive airway disease*, *obstructive pulmonary disease*, or *COPD*. Trials were not excluded on the basis of language. The search was further augmented by scanning references of identified articles and reviews.

### Study Selection

Two investigators independently evaluated studies for inclusion. The observed percentage agreement between raters for the assessment of inclusion was calculated using the  $\kappa$ -statistic.<sup>18</sup> Trials were considered if they were randomized, placebo-controlled trials of  $\beta_2$ -agonist use in patients with asthma or COPD.

Single-dose trials were included if they provided extractable data on heart rate or potassium concentrations. Heart rates in the trials were recorded at rest, with measurements made manually, from an ECG, or as a mean value from a cardiac monitor. Longer duration trials were included if they reported at least one *adverse cardiovascular event*, which was defined as sinus or ventricular tachycardia, atrial fibrillation, syncope, myocardial infarction, congestive heart failure, cardiac arrest, or sudden death. Trials were included even if they allowed for open-label "rescue"  $\beta_2$ -agonist use in both the treatment and placebo groups.

### Assessment of Validity

The methodological quality of each included trial was assessed.<sup>19</sup> A score of A, B, or C was given to trials using the following factors: (1) Was the trial randomized, and if so, was the randomization procedure adequate? (2) Were the patients and people administering the treatment blind to the intervention? (3) Did trials utilize a crossover design or were parallel groups studied? Two reviewers independently assessed quality scores, and interrater agreement was calculated using the  $\kappa$ -statistic.

### Data Extraction and Synthesis

Two reviewers independently extracted data from the selected articles, reconciling differences by consensus. In addition, attempts were made to contact the investigators to obtain additional information concerning cardiovascular events.

For single-dose studies, the group mean heart rates and potassium concentrations were measured for active treatment and placebo, and the placebo effect was subtracted from the treatment effect. The net treatment effects for each trial then were pooled to obtain a weighted mean difference, using the random-effects model for continuous outcomes.<sup>20</sup> The random-effects model was used because it accounts for the possibility of significant interstudy heterogeneity. The analyses were performed using a software package (Meta View, version 4.1; Cochrane Library software, Update Software; Oxford, UK). In order to test for interstudy variability, the  $\chi^2$  value was calculated for the assumption of homogeneity, with the statistical significance set at  $p < 0.1$ .

For longer duration trials, the rate of adverse cardiovascular events was measured for therapy with  $\beta_2$ -agonists and for placebo in each trial, and the relative risk (RR) was calculated as the ratio of the treatment event rate to the placebo event rate. Only trials that reported at least one event could be used in the calculation of RR. Adverse events recorded included sinus and ventricular tachycardia, syncope, atrial fibrillation, congestive heart failure, myocardial infarction, cardiac arrest, and sudden death. It was chosen to include sinus tachycardia because it is an arrhythmia that can herald a poor prognosis when associated with underlying cardiac conditions.<sup>21</sup> Mild adverse outcomes that were not recorded included palpitations, chest pain, hypertension, and asymptomatic abnormalities found on ECG such as ectopic beats, ischemic changes, or conduction abnormalities.

The RRs for cardiovascular events in each trial were pooled using the fixed-effects model for dichotomous outcomes.<sup>22</sup> The data were analyzed separately for sinus tachycardia, which was considered to be a minor event, and for all other events, which were considered to be more clinically significant. The fixed-effects model was chosen because minimal heterogeneity was noted in the analysis. The results then were compared to the random-effects model.

## RESULTS

### Search Results

The electronic database search identified approximately 5,000 articles, and, of these, 185 were randomized, placebo-controlled trials of  $\beta_2$ -agonist use in patients with obstructive airway disease. After scanning references from selected articles, an additional six potentially relevant trials were identified. Of these 191 studies, 13 single-dose trials and 20 longer duration trials met the inclusion criteria. The  $\kappa$ -statistic for interrater agreement on study eligibility was 0.98 (95% confidence interval [CI], 0.96 to 1.00). Consensus was reached on the remaining trials. Trials were excluded for the following reasons: 38 single-dose trials did not provide extractable data on heart rate or potassium concentrations; 115 longer duration trials did not report adverse cardiovascular events or did not provide extractable data; and 5 trials provided data on participants who were already included in the analysis.

### Trial Characteristics

The characteristics of each study can be found in Table 1. Of the single-dose trials, seven were of asthma, five were on COPD and one reported data on both.<sup>23–35</sup> There were a total of 232 participants, with a mean age of 56.6 years. Of the longer duration trials, 14 were of asthma and 6 were of COPD.<sup>36–55</sup> There was a total of 6,623 participants with a mean age of 52.2 years in these trials, which ranged in duration from 3 days to 1 year with a mean trial duration of 4.7 months. All but one trial allowed for the use of rescue  $\beta_2$ -agonist use in both the treatment and placebo groups.

### Methodological Quality of Included Studies

All of the single-dose trials were double-blind or single-blind crossover trials that received a B quality score. Of the longer duration trials, 15 were double-blind, parallel-group studies that received an A quality score, and 5 were single-blind or double-blind crossover trials that received a B score. The  $\kappa$  score for interrater agreement on methodological quality scores was 1.00.

### Quantitative Data Synthesis

A single dose of a  $\beta_2$ -agonist caused an increase in heart rate of 9.12 beats/min (95% CI, 5.32 to 12.92) compared to placebo (Fig 1). The administration of a single dose also caused a reduction in potassium concentration by 0.36 mmol/L (95% CI, 0.18 to 0.54) compared to placebo (Fig 2).

In the longer duration trials, treatment with a

$\beta$ -agonist was associated with a significantly increased risk for adverse cardiovascular events (RR, 2.54; 95% CI, 1.59 to 4.05) compared to that for placebo (Fig 3). These results were highly significant ( $p = 0.00001$ ). The random-effects method did not give significantly different results (RR, 2.25; 95% CI, 1.37 to 3.69). The majority of events recorded after  $\beta$ -agonist use were due to sinus tachycardia. The risk for sinus tachycardia was significantly increased (RR, 3.06; 95% CI, 1.7 to 5.5) compared to that when receiving placebo. The major adverse events recorded included ventricular tachycardia, atrial fibrillation, syncope, congestive heart failure, myocardial infarction, cardiac arrest, and sudden death. The RR attributed to these major cardiovascular events was 1.61 (95% CI, 0.76 to 3.42), which did not reach statistical significance.

### Interstudy Variability

There was evidence for significant interstudy variance in the analysis of heart rate and potassium concentrations, with  $p$  values  $< 0.001$ . No evidence of heterogeneity was noted in the analysis of RR, with a  $p$  value for heterogeneity of 0.93.

## DISCUSSION

In summary, the initiation of  $\beta_2$ -agonist therapy was associated with significant increases in heart rate and reductions in potassium concentrations, which are known to be common systemic effects of  $\beta$ -adrenergic stimulation, compared to placebo. With continued treatment, the rate of cardiovascular events was increased compared to placebo, with a significant increase in sinus tachycardia and a non-significant trend toward an increase in major cardiovascular events. It is possible that  $\beta_2$ -agonists could precipitate arrhythmias, ischemia, and congestive heart failure through the activation of  $\beta$ -adrenergic stimulation.<sup>8,56</sup>

Case-control studies have found an association between  $\beta_2$ -agonist use and an increase in cardiovascular morbidity and mortality.  $\beta_2$ -agonists have been associated with an increased risk for fatal and non-fatal myocardial infarction (adjusted OR, 1.67; 95% CI, 1.07 to 2.60), with higher risks seen for those with a history of cardiovascular disease (adjusted OR, 3.22; 95% CI, 1.63 to 6.35) and for new users of  $\beta$ -agonists (adjusted OR, 7.32; 95% CI, 2.34 to 22.8).<sup>11</sup> Inhaled  $\beta$ -agonist use also has been associated with an increased risk for heart failure (adjusted OR, 3.41; 95% CI, 1.99 to 5.86) and cardiomyopathy (adjusted OR, 3.2; 95% CI, 1.4 to 7.1), with no difference found between the development of idiopathic or ischemic cardiomyopathy.<sup>12,14,15</sup>  $\beta$ -Agonist

Table 1—Trial Characteristics\*

Study/Year	Design/Duration	Inclusion and Exclusion Criteria	Participants, No.	Dropout Rate, %	Age, † yr	Active Interventions	Outcomes Measured	Comments
Aalbers et al <sup>36</sup> /2002	Double-blind, parallel-group/ 3 mo	Inclusion: COPD Exclusion: asthma, allergic rhinitis, eosinophilia, recent respiratory tract infection, heart disease, other significant illness	692	17	62	Inhaled formoterol	FEV <sub>1</sub> , symptoms rescue $\beta$ -agonist use	Allowed for rescue $\beta$ -agonist use
Anderson et al <sup>37</sup> /1979	Double-blind, crossover/ <sup>3</sup> d	Inclusion: asthma Exclusion: none listed	17	0	52	Inhaled fenoterol, terbutaline	Peak expiratory flow, symptoms	Allowed for rescue $\beta$ -agonist use
Bennett et al <sup>27</sup> /1994	Double-blind, crossover/ single-dose	Inclusion: mild asthma Exclusion: significant other medical problems	12	0	29–54	Inhaled salmeterol, salbutamol	Pulse, potassium* level, FEV <sub>1</sub> , BP	
Bensch et al <sup>38</sup> /2001	Double-blind, parallel-group/ 3 mo	Inclusion: mild to moderate asthma Exclusion: clinically significant, uncontrolled major organ system dysfunction of respiratory or cardiovascular system	541	15	35	Inhaled formoterol, albuterol	FEV <sub>1</sub> , asthma symptoms, rescue $\beta$ -agonist use	Allowed for rescue $\beta$ -agonist use
Boyd <sup>39</sup> /1995	Double-blind, parallel-group/ 3 mo	Inclusion: severe, chronic asthma Exclusion: concurrent uncontrolled systemic disease, recent acute respiratory infection	181	34	47	Inhaled salmeterol	Peak expiratory flow, symptoms, rescue $\beta$ -agonist use	Allowed for rescue $\beta$ -agonist use
Braden et al <sup>24</sup> /1998	Double-blind, crossover/ single-dose	Inclusion: asthma, nonsmoking Exclusion: recent $\beta$ -agonist use or caffeine-containing beverages	8	0	32	Nebulized terbutaline	Pulse, potassium, M-mode echocardiography	
Braun and Levy <sup>25</sup> /1991	Double-blind, crossover/ single-dose	Inclusion: COPD Exclusion: cardiovascular, renal, hepatic, endocrine, metabolic or other systemic disease, urinary retention, prostatic hypertrophy, or glaucoma	72	0	61	Inhaled albuterol	Pulse, BP, FEV <sub>1</sub> , FVC	Inhaled ipratropium also studied
Buch and Bundgaard <sup>26</sup> /1984	Double-blind, crossover/ single-dose	Inclusion: asthma, treated with inhaled $\beta$ -agonists Exclusion: recent exacerbation	8	0	38	Nebulized or IM terbutaline	Pulse, BP, echocardiography	
Burgess et al <sup>27</sup> /1998	Double-blind, crossover/ single-dose	Inclusion: mild-to-moderate asthma Exclusion: COPD	20	0	30	Inhaled formoterol	Pulse, potassium level, BP, ECG changes, glucose, FEV <sub>1</sub>	



**Table 1—Continued\***

Study/Year	Design/Duration	Inclusion and Exclusion Criteria	Participants, No.	Dropout Rate, %	Age, † yr	Active Interventions	Outcomes Measured	Comments
Burgess et al <sup>27</sup> /1998	Double-blind, crossover/ single-dose crossover/ single-dose	Inclusion: mild asthma Exclusion: regular use of $\beta$ -agonist Inclusion: COPD with preexisting cardiac arrhythmias and hypoxemia Exclusion: corticosteroid use, recent respiratory tract infection, myocardial infarction, decompensated heart failure, unstable angina, or known severe arrhythmia	8	0	21–26	Inhaled formoterol under conditions of normoxia and hypoxia Inhaled formoterol, salmeterol	Pulse, potassium, BP Holter monitor, potassium level	Hypoxia induced by breathing nitrogen/oxygen mixture
Cazzola et al <sup>29</sup> /1998	Single-blind, crossover/ single-dose	Inclusion: COPD with preexisting cardiac arrhythmias and hypoxemia Exclusion: corticosteroid use, recent respiratory tract infection, myocardial infarction, decompensated heart failure, unstable angina, or known severe arrhythmia	12	0	60	Inhaled formoterol, salmeterol	Holter monitor, potassium level	
Chan et al <sup>30</sup> /1988	Double-blind, crossover/ single-dose	Inclusion: stable COPD Exclusion: cardiac disease	10	0	67	Oral terbutaline	Pulse, right and left ventricular ejection fractions, FEV <sub>1</sub> , FVC	
Chapman et al <sup>40</sup> /2002	Double-blind, parallel-group/ 6 mo	Inclusion: COPD Exclusion: respiratory tract infection, recent COPD hospitalization, concurrent respiratory disorders, pregnancy	408	12	Over 40	Inhaled salmeterol	FEV <sub>1</sub> , symptoms, rescue $\beta$ -agonist use	All patients were receiving inhaled anticholinergic therapy; all owed for rescue $\beta$ -agonist use
Dahl et al <sup>42</sup> /1991	Double-blind, parallel-group/ 4 wk	Inclusion: mild-to-moderate reversible airways disease Exclusion: lower respiratory tract infection, corticosteroid use, hypokalemia, concurrent serious illness	1,068	11	42	Inhaled salmeterol	Symptoms, rescue $\beta$ -agonist use, peak expiratory flow, pulse, BP	Allowed for rescue $\beta$ -agonist use
Dahl et al <sup>43</sup> /2001	Double-blind, parallel-group/ 3 mo	Inclusion: COPD Exclusion: asthma, respiratory tract infection, long-term oxygen therapy, corticosteroid use, oral $\beta$ -agonist use	780	11	64	Inhaled formoterol	FEV <sub>1</sub> , symptoms	Inhaled ipratropium also studied; allowed for rescue $\beta$ -agonist use
Donohue et al <sup>44</sup> /2002	Double-blind, parallel-group/ 6 mo	Inclusion: COPD Exclusion: asthma, allergic rhinitis, eosinophilia, recent respiratory tract infection	623	19	65	Inhaled salmeterol	FEV <sub>1</sub> , symptoms, rescue $\beta$ -agonist use	Inhaled tiotropium also studied; allowed for rescue $\beta$ -agonist use
D'Urzo et al <sup>41</sup> /2001	Double-blind, parallel-group/ 6 mo	Inclusion: asthma Exclusion: uncontrolled pulmonary or systemic disease, psychological conditions	911	22	46	Nebulized salmeterol	Asthma exacerbations	Allowed for rescue $\beta$ -agonist use

Table 1—Continued\*

Study/Year	Design/Duration	Inclusion and Exclusion Criteria	Participants, No.	Dropout Rate, %	Age, † yr	Active Interventions	Outcomes Measured	Comments
Fitzpatrick et al <sup>45</sup> /1990	Double-blind, crossover/2 wk	Inclusion: nocturnal asthma Exclusion: none listed	20	15	39	Inhaled salmeterol, salbutamol	Peak expiratory flow rates, sleep quality	Allowed for rescue β-agonist use
Hall et al <sup>31</sup> /1994	Single-blind, crossover/ single-dose	Inclusion: COPD with severe chronic airflow obstruction Exclusion: theophylline use, history of arrhythmias or heart disease	22	0	67	Nebulized salbutamol	Heart rhythm, potassium level	
Jartti et al <sup>32</sup> /1997	Double-blind, crossover/ single-dose	Inclusion: children with bronchial asthma Exclusion: diabetes mellitus, cardiovascular, GI, urinary tract, CNS, or peripheral nervous system disease	8	0	11	Inhaled salbutamol	Pulse, beat-to-beat variability of heart rate and BP	
Marlin et al <sup>33</sup> /1978	Double-blind, crossover/ single-dose	Inclusion: asthma or chronic bronchitis Exclusion: none listed	12	0	32–72	Inhaled fenoterol	Pulse, FEV <sub>1</sub>	Ipratropium also studied
Milgrom et al <sup>46</sup> /2001	Double-blind, parallel-group/ 3 wk	Inclusion: children with asthma Exclusion: allergy to study medications, lower respiratory tract infection, abnormal ECG	338	15	9	Nebulized levalbuterol, racemic albuterol	FEV <sub>1</sub> , FVC, symptoms	Allowed for rescue β-agonist use
Nathan et al <sup>47</sup> /1995	Double-blind, parallel-group/ 3 mo	Inclusion: asthma Exclusion: smoking history	556	1	12–73	Inhaled salmeterol, albuterol	Adverse events, pulse, BP	Allowed for rescue β-agonist use
Nielsen et al <sup>48</sup> /1999	Double-blind, parallel-group/ 2 wk	Inclusion: steroid-dependent asthma Exclusion: stable asthma when corticosteroid tapered off	34	0	44	Inhaled salmeterol	FEV <sub>1</sub> , peak expiratory flow, rescue β-agonist use, minimal accepted dose of corticosteroid	Allowed for rescue β-agonist use
Pearlman et al <sup>49</sup> /1999	Double-blind, parallel-group/ 4 wk	Inclusion: asthma Exclusion: life-threatening asthma, hypersensitivity to study drugs, smoking, corticosteroid use	136	5	27–35	Inhaled salmeterol, with or without fluticasone	FEV <sub>1</sub> , peak expiratory flow, symptoms	Allowed for rescue β-agonist use
Rennard et al <sup>50</sup> /2001	Double-blind, parallel-group/ 3 mo	Inclusion: COPD Exclusion: recent pulmonary infection, significant cardiovascular disease, malignancy, abnormal ECG	405	18	64	Inhaled salmeterol	FEV <sub>1</sub> , FVC, symptoms, exacerbations, adverse events	Inhaled ipratropium also studied; allowed for rescue β-agonist use
Richter et al <sup>51</sup> /2000	Single-blind, cross-over/1 y	Inclusion: moderate-to-severe asthma Exclusion: significant nonrespiratory illnesses, pregnancy	80	9	48	Inhaled salbutamol, fenoterol	Asthma exacerbations, symptoms, rescue β-agonist use, peak expiratory flow	Allowed for rescue β-agonist use

**Table 1—Continued\***

Study/Year	Design/Duration	Inclusion and Exclusion Criteria	Participants, No.	Dropout Rate, %	Age,† yr	Active Interventions	Outcomes Measured	Comments
Rossi et al <sup>52</sup> /2002	Double-blind, parallel-group/1 yr	Inclusion: COPD Exclusion: uncontrolled pulmonary or systemic disease	854	27	63	Inhaled formoterol	FEV <sub>1</sub> , symptoms, rescue $\beta$ -agonist use	Oral theophylline also studied; allowed for rescue $\beta$ -agonist use
Siegel et al <sup>53</sup> /1985	Double-blind, parallel-group/2 wk	Inclusion: asthma Exclusion: oral corticosteroids, concomitant $\beta$ -blockers, bronchiectasis, cystic fibrosis, significant concurrent disease, recent oral $\beta$ -agonists	45	13	18–55	Oral procaterol	FEV <sub>1</sub> , FVC, symptoms	Allowed for rescue $\beta$ -agonist use
Spector and Garza Gomez <sup>54</sup> /1977	Double-blind, crossover/3 d	Inclusion: asthma Exclusion: cardiovascular, hepatic, renal, endocrinologic, or metabolic disease, other than diabetes mellitus	24	33	14–65	Nebulized albuterol, isoproterenol	FEV <sub>1</sub> , FVC, pulse	Allowed for rescue $\beta$ -agonist use
Vathenen et al <sup>54</sup> /1988	Double-blind, crossover/single-dose	Inclusion: chronic bronchitis with severe airflow limitation Exclusion: use of corticosteroids or nebulized bronchodilator	30	0	63	Inhaled albuterol	Pulse, heart rhythm, FEV <sub>1</sub> , walking distance, tremor, oxygen saturation, symptoms	
Wong et al <sup>55</sup> /1990	Double-blind, crossover/single-dose	Inclusion: asthma Exclusion: other important disorders	10	0	18–40	Inhaled fenoterol, salbutamol, terbutaline	Pulse, potassium, FEV <sub>1</sub> , bronchial reactivity to histamine	
Yates et al <sup>55</sup> /1995	Double-blind, crossover/2 wk	Inclusion: mild stable asthma, nonsmoking Exclusion: steroid use within 4 mo	17	0	26	Inhaled formoterol	PC <sub>20</sub> (methacholine), FEV <sub>1</sub>	Rescue ipratropium

\*PC<sub>20</sub> = provocative concentration of a substance causing a 20% fall in FEV<sub>1</sub>.

†Values given as mean or range.



**Cardiovascular effects of beta-agonist use**  
**Single dose - Heart rate, beats per minute (treatment minus placebo)**

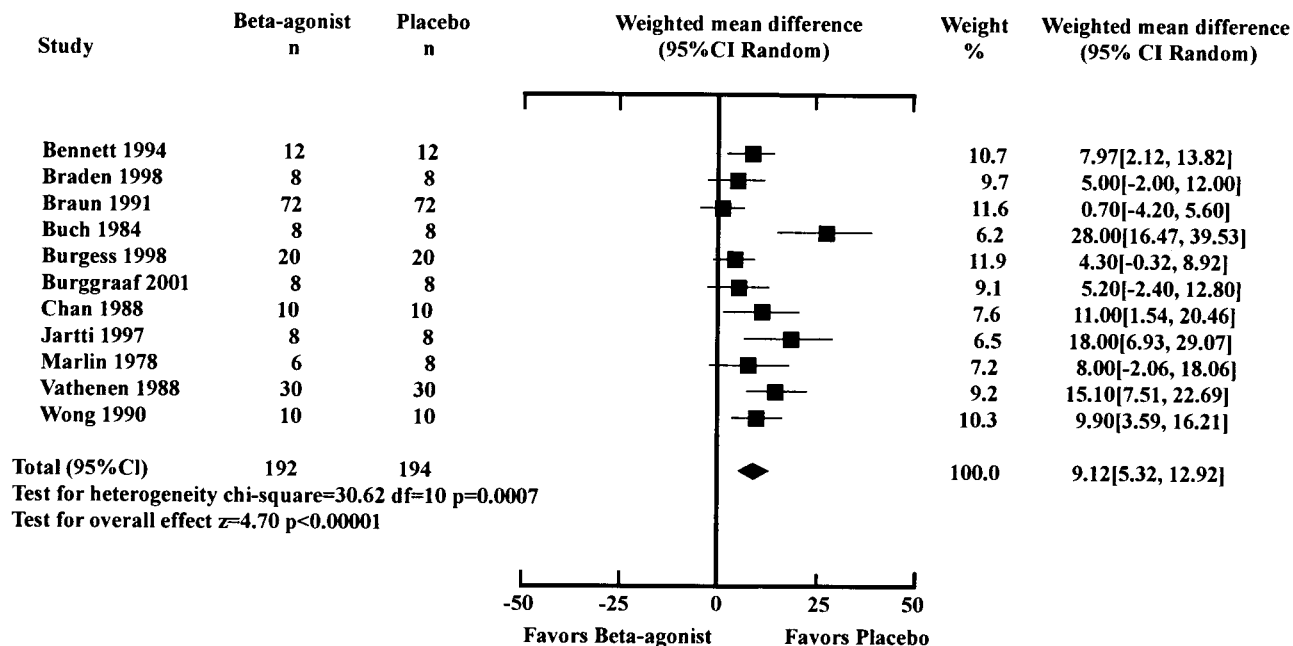


FIGURE 1. Cardiovascular effects of  $\beta$ -agonist use. Heart rate in single-dose trials. df = degrees of freedom.

use also has been linked to cardiac arrest (adjusted OR, 1.9; 95% CI, 1.1 to 3.3) and acute cardiac death, with higher risks associated with nebulized and oral treatment (adjusted OR, 2.4; 95% CI, 1.0 to 5.4)

compared to metered-dose inhaler treatment (adjusted OR, 1.2; 95% CI, 0.5 to 2.7).<sup>13,16</sup> These observational studies demonstrate that  $\beta$ -agonist use is associated with an increased risk for cardiovascular

**Cardiovascular effects of beta-agonist use**  
**Single dose - Potassium, mmol/L (treatment minus placebo)**

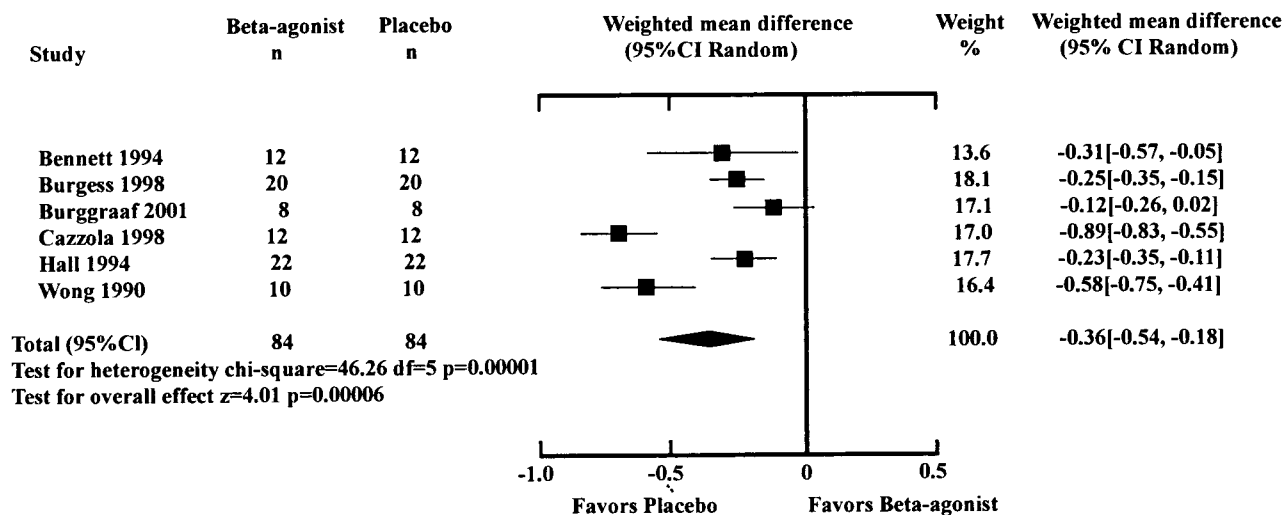


FIGURE 2. Cardiovascular effects of  $\beta$ -agonist use. Potassium concentrations in single-dose trials. See Figure 1 for abbreviation not used in the text.

**Cardiovascular effects of beta-agonist use**  
**Longer duration - cardiovascular events (treatment/placebo)**

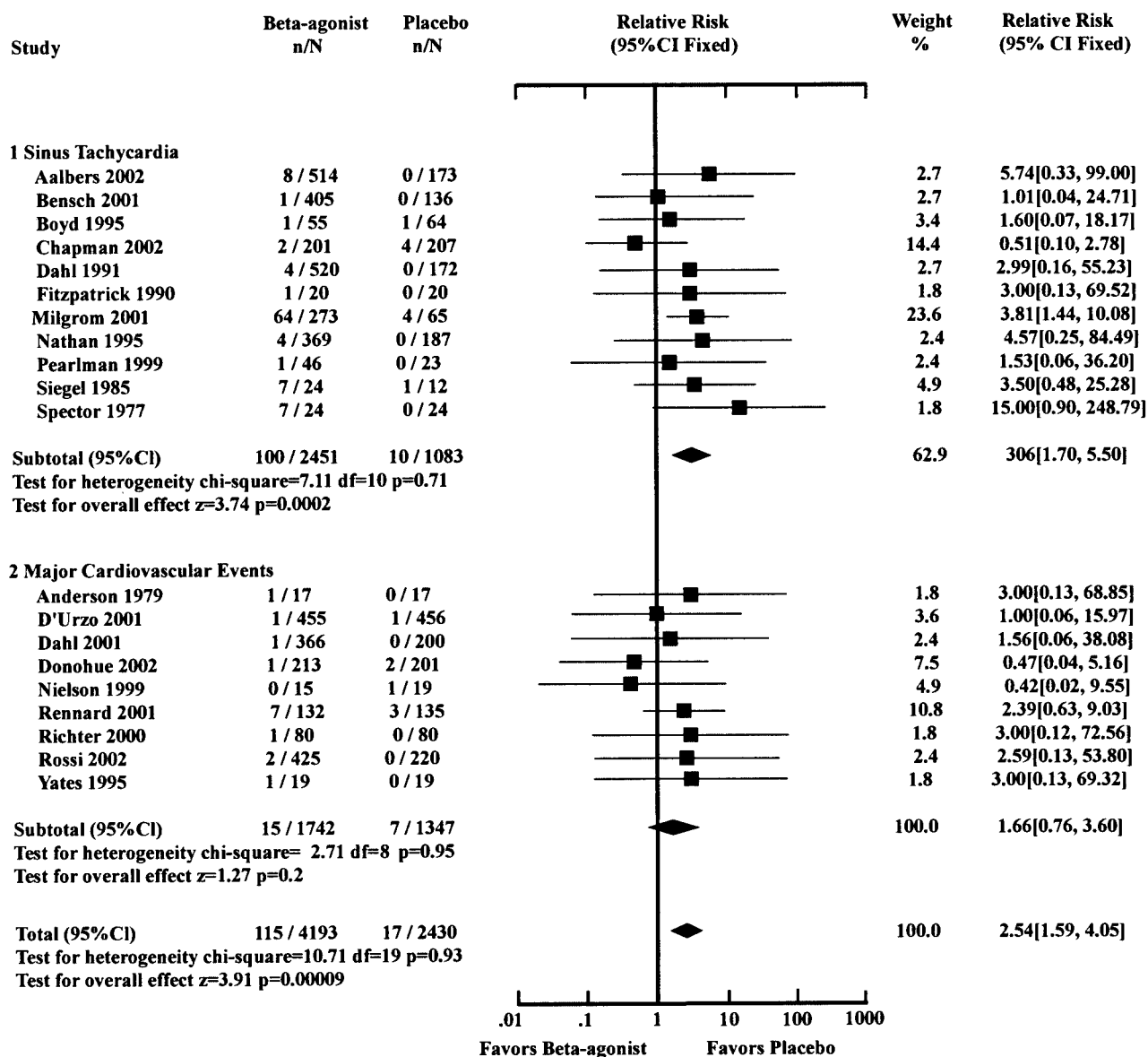


FIGURE 3. Cardiovascular effects of  $\beta$ -agonist use. Cardiovascular events in longer duration trials. See Figure 1 for abbreviation not used in the text.

events, even when confounding variables are adjusted for. The results of this meta-analysis provide evidence to indicate that the association seen in observational studies may be a causal one.

Over the past 40 years, case reports of adverse cardiovascular events, including ischemia, myocardial depression, atrial fibrillation, ventricular arrhythmia, fatal myocardial contraction band necrosis, and sudden cardiac death, resulting from  $\beta_2$ -agonist use have accumulated.<sup>9,57-62</sup>  $\beta_2$ -Agonists also have been shown to increase ventricular and atrial ectopy,

and to prolong the corrected Q-T interval on ECGs.<sup>29,35,63-67</sup> These are all physiologic effects of  $\beta_2$ -receptor stimulation in the heart and skeletal muscle.<sup>8</sup>

$\beta$ -Adrenergic stimulation increases heart rate and myocardial oxygen demand, and causes direct myocardial injury or necrosis that could lead to ischemia, progression of congestive heart failure, or sudden death.<sup>1,8,61</sup> Sinus tachycardia is a supraventricular arrhythmia that can signal severe underlying pathology and is associated with a poor prognosis in the

presence of underlying ischemia, myocardial infarction, or congestive heart failure.<sup>21</sup> Tachycardia not only is a marker of sympathetic stimulation, which in itself is associated with a poor cardiovascular prognosis, but also directly contributes to cardiac work and strain.<sup>68</sup> Elevated heart rate has been shown to be a strong independent risk factor for the development of cardiomyopathy, coronary artery disease, fatal myocardial infarction, sudden death, cardiovascular mortality, and total mortality.<sup>69–76</sup>

Hypokalemia occurs with  $\beta_2$ -adrenergic stimulation as a result of intracellular shifts of potassium into skeletal muscle.<sup>8</sup> Hypokalemia has been associated with an increased risk for ventricular tachycardia and fibrillation in susceptible patients.<sup>77</sup> In patients with obstructive airway disease, serum potassium levels could be decreased further with the use of corticosteroids and diuretics, and the cardiac effects of hypokalemia could be aggravated by underlying hypoxemia.<sup>8,28,78,79</sup>

The  $\beta$ -adrenergic system has a very tight negative feedback mechanism as an adaptive response to either stimulation or blockade of the receptors.<sup>2</sup> Stimulation results in the uncoupling and internalization of the receptors, which is known as *desensitization*, and it can occur within a time range of minutes to hours.<sup>2</sup> This is followed by a decrease in receptor density and receptor gene expression, which is known as *downregulation*, and it develops within hours of stimulation.<sup>80–82</sup> This tolerance to adrenergic stimulation could explain why the highest risk for adverse cardiovascular events is seen during the initiation of  $\beta_2$ -agonist therapy.<sup>11,14</sup> Conversely, when stimulation is stopped, the receptor begins to recover within a few hours, indicating that the risk for cardiac stimulation is present with continued  $\beta_2$ -agonist use, even when used on a relatively regular basis.<sup>83,84</sup>

This meta-analysis has several limitations that make it difficult to reach definitive conclusions. There was a marked heterogeneity noted in the longer duration trials, despite the fact that no heterogeneity was seen in the results. For example, there was a wide range in study size and duration, the mean age of participants, medications used, and documentation of adverse events. In addition, most of the trials reported a low incidence of adverse events, with large CIs that did not reach statistical significance. Approximately one half of the adverse cardiac events occurred in one trial.<sup>46</sup> However, if this trial were excluded from the analysis, the pooled results would still be significant (RR, 2.15; 95% CI, 1.26 to 3.65).

This analysis provides evidence that  $\beta_2$ -agonists, when administered regularly for a few days or for up to 1 year, may increase the risk for adverse cardio-

vascular events compared to placebo. However, it is not possible to estimate the absolute risk attributed to treatment, as only those trials with at least one event were included in the analysis. Furthermore, almost all of the trials analyzed allowed for as-needed  $\beta_2$ -agonist use in the placebo group, which could potentially underestimate the true risk of  $\beta_2$ -agonist use compared to no use at all. It is difficult to assess the magnitude of risk for those patients with underlying cardiac conditions or risk factors, as most of the trials in this analysis excluded patients with concomitant cardiovascular disease, abnormal ECG findings, or medical illnesses in general. No information was provided in the trials on concomitant  $\beta$ -blocker use, which could potentially decrease the cardiac risks of  $\beta_2$ -agonist therapy.

In this analysis, adverse cardiovascular events were analyzed in two subgroups. Sinus tachycardia was considered to be a minor event, and all other fatal and nonfatal events were combined in the category of major events. The power of the study was not large enough to perform subgroup analyses for each specific cardiac cause. Even when major events were combined, the RR of 1.66 did not reach statistical significance. Despite these limitations, we believe that this analysis should heighten concern over the cardiovascular safety of  $\beta_2$ -agonist use in patients with obstructive airway disease.

The competing risks and benefits of  $\beta_2$ -agonist use has been a topic of much discussion.<sup>85–88</sup>  $\beta_2$ -agonists have been the mainstay of therapy for obstructive lung diseases since the 1960s, with studies demonstrating sustained improvements in peak flows and respiratory symptoms.<sup>86</sup> Evidence that  $\beta_2$ -agonist use is associated with an increase in morbidity and mortality also has been accumulating over the past 50 years.<sup>8,89–91</sup> Originally, most of the deaths were thought to be due to cardiac failure with associated underlying ventricular arrhythmias.<sup>90,91</sup> More recently, evidence has been accumulating<sup>92–96</sup> indicating that the regular use of  $\beta_2$ -agonists also results in tolerance to its bronchodilator and nonbronchodilator effects, and may lead to an increase in asthma exacerbations and deaths.

Once a therapeutic practice is considered to be the standard of care, it often takes numerous studies and many years, if not decades, to transition into a more evidence-based practice. For example, standards of care in the treatment of congestive heart failure have changed drastically since studies showed that  $\beta$ -blockers are beneficial instead of harmful, as originally was thought, and that  $\beta_1$ -agonists such as dobutamine can temporarily improve symptoms but at the cost of increased mortality.<sup>1,97</sup> Many elderly patients with underlying cardiovascular diseases such as congestive heart failure have concomitant obstructive

tive airway disease. Despite clear evidence that  $\beta$ -blockers reduce mortality in many cardiac conditions, these agents are considered to be contraindicated in patients with obstructive airway disease due to the potential risk for bronchospasm. However, new evidence has shown that cardioselective  $\beta$ -blockers are safe in patients with asthma and COPD, and may actually be beneficial by enhancing sensitivity to endogenous or exogenous  $\beta$ -adrenergic stimulation.<sup>98,99</sup>

This analysis reinforces the accumulating evidence that  $\beta_2$ -agonist use leads to an increased risk for adverse cardiovascular events in patients with obstructive airway disease. This is of special concern for those patients with underlying cardiac conditions. In contrast, cardioselective  $\beta$ -blocker therapy is safe in patients with obstructive lung disease and is associated with significant reductions in cardiovascular mortality. To help clarify the issue, long-term trials in patients with obstructive airway disease and concomitant heart disease are needed to evaluate the safety and efficacy of  $\beta_2$ -agonist use compared to therapies using other substances, such as ipratropium, corticosteroids, or  $\beta$ -blockers. Until then, the available evidence needs to be examined closely in an attempt to reassess whether  $\beta_2$ -agonists should be administered to patients with obstructive airway disease, with or without underlying cardiovascular conditions.

**ACKNOWLEDGMENT:** We thank Donald Miller for his graphical assistance, and Christopher Stave for coordinating the trials search.

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# Cardiovascular Effects of $\beta$ -Agonists in Patients With Asthma and COPD: A Meta-Analysis

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*Chest* 2004;125:2309-2321

DOI: 10.1378/chest.125.6.2309

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