Cardioselective β-Blockers in Patients with Reactive Airway Disease: A Meta-Analysis

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

Objective: To assess the effect of cardioselective β-blockers on respiratory function of patients with reactive airway disease.

Data Sources: Comprehensive searches of the EMBASE, MEDLINE, and CINAHL databases from 1966 to May 2001 and scanning of references of the identified articles and related reviews.

Study Selection: Randomized, blinded, placebo-controlled trials that studied the effects of cardioselective β-blockers on FEV_1, symptoms, and the use of inhaled β_2-agonists in patients with reactive airway disease were selected. Interventions studied were the administration of a cardioselective β-blocker and administration of β_2-agonist after the study drug.

Data Extraction: Outcomes measured were the change in FEV_1 from baseline, the number of patients with respiratory symptoms, and the use of inhaled β_2-agonists with active treatment compared with placebo.

Data Synthesis: Nineteen studies on single-dose treatment and 10 studies on continued treatment were included. Administration of a single dose of a cardioselective β-blocker was associated with a 7.46% (95% CI, 5.59% to 9.32%) decrease in FEV_1 and a 4.63% (CI, 2.47% to 6.78%) increase in FEV_1 response to β-agonist compared with placebo, with no increase in symptoms. Trials lasting from 3 days to 4 weeks produced no significant change in FEV_1 (−0.42% [CI, −3.74% to 2.91%]), symptoms, or inhaler use compared with placebo but maintained an 8.74% (CI, 1.96% to 15.52%) increase in β-agonist response. No significant treatment effect in terms of FEV_1 was found in patients with concomitant chronic obstructive pulmonary disease, whether single doses (change in FEV_1, −5.28% [CI, −10.03% to −0.54%]) or continued treatment (change in FEV_1, 1.07% [CI, −3.3% to 5.44%]) was given.

Conclusions: Cardioselective β-blockers do not produce clinically significant adverse respiratory effects in patients with mild to moderate reactive airway disease. The results were similar for patients with concomitant chronic airways obstruction. Given their demonstrated benefit in such conditions as heart failure, cardiac arrhythmias, and hypertension, cardioselective β-blockers should not be withheld from patients with mild to moderate reactive airway disease.

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For author affiliations, see end of text.

See editorial comment on pp 766-767.

β-Adrenergic blocking agents, or β-blockers, are indicated in the management of angina pectoris, myocardial infarction, hypertension, congestive heart failure, cardiac arrhythmia, and thyrotoxicosis and are given to reduce perioperative complications (1–13). Despite clear evidence of the effectiveness and mortality benefit of these drugs, clinicians are often hesitant to administer them in patients with some common conditions for fear of adverse reactions (14–17).

Many patients with reactive airway disease, with or without a chronic obstructive component, have concomitant conditions such as hypertension or cardiac arrhythmias, which necessitate the use of β-blockers. However, review articles and practice guidelines usually list asthma and chronic obstructive pulmonary disease (COPD) as contraindications to β-blocker use, citing cases of acute bronchospasm during administration of noncardioselective β-blockers (6, 10, 18–22). Cardioselective β-blockers, or β_1-blockers, have greater than 20 times more affinity for β_1 receptors than for β_2 receptors and in theory should pose much less risk for bronchoconstriction (23).

We used data from randomized, blinded, placebo-controlled trials to evaluate the effect of cardioselective β_1-blockers on respiratory function in patients with reactive airway disease (defined as asthma or COPD with a reversible obstructive component). We also sought to evaluate the respiratory response to β_2-agonists administered after β_1-blockers or after placebo in the same participants. This analysis has already been published as a review in the Cochrane Library (24).

METHODS

Patients

We chose to evaluate only patients with documented reactive airway disease because these patients are thought to be particularly susceptible to the adverse respiratory effects of β-blockers. Patients with COPD are generally at greater risk for ischemic heart disease than are patients with asthma and thus may benefit more from the use of β-blockers. This study evaluates a subgroup of patients with a documented chronic obstructive component of disease but was not designed to make recommendations about patients with COPD. A recent meta-analysis evaluated the use of cardioselective β-blockers in patients with COPD, given as a single dose or as continued treatment (25). Pooled data from 19 trials demonstrated no adverse effect on FEV_1 or respiratory symptoms for β_1-blockers compared to placebo, even in patients with severe chronic airway obstruction.

Search Strategy

A search was performed to identify all relevant published clinical trials that addressed the effects of cardioselective β-blockers on airway function in patients with reactive airway disease. Two investigators jointly developed strategies with the help of an information service librarian

Context

Although β-blockers improve clinical outcomes in many patients with cardiovascular disease, clinicians sometimes avoid these agents in patients with concomitant lung disease because they fear precipitation of acute bronchospasm.

Contribution

This meta-analysis of 29 randomized trials shows that cardioselective β-blockers (β_1-blockers), given for a few days to a few weeks, do not significantly worsen pulmonary function or respiratory symptoms and do not lead to increased use of inhalers in patients with mild to moderate reactive (reversible) airway disease.

Cautions

The studies in this meta-analysis were short, evaluated only cardioselective β-blockers, and did not include patients with severe or irreversible airway disease.

–The Editors

and the Cochrane Airways Group Trial Search Coordinator. The EMBASE, MEDLINE, and CINAHL databases were searched comprehensively to identify all relevant clinical trials in humans published between 1966 and May 2001. The search was performed by using the Cochrane Airways Group registry to identify randomized, blinded, placebo-controlled trials of reactive airways disease. Terms used in the search were *asthma**, *bronchial hyperreactivity**, *respiratory sounds**, *wheez**, *obstructive lung disease**, and *obstructive airway disease**. Trials of β-blockers were sought by using the terms *adrenergic antagonist**, *sympatholytic**, and *adrenergic receptor block**. Trials were not excluded on the basis of language. The search was further augmented by scanning references of identified articles, reviews, and abstracts at clinical symposia.

Study Selection

Two investigators independently evaluated studies for inclusion. In choosing articles, investigators were blinded to results but not to journal, author, or institution of studies. The observed interrater agreement for the assessment of inclusion was calculated as a percentage. For all clinical trials identified from the search, investigators determined whether the β-blocker used was cardioselective and whether it was considered to have intrinsic sympathomimetic activity (1, 26–36). Studies were evaluated if intravenous or oral cardioselective β-blockers were administered as a single dose or as continued treatment lasting 3 days or longer.

Single-dose trials were included if 1) FEV_1 at rest was reported, either as liters or as a percentage of the normal predicted value at baseline and at follow-up; 2) β_2-agonists were withheld for at least 8 hours before initial FEV_1 measurement; 3) patients were not selected on the basis of previous response to β-blockers; 4) the study was randomized, placebo-controlled, and single- or double-blinded; and 5) only patients with documented reactive airway disease were included. Reactive airway disease was demonstrated by a mean increase of at least 15% in FEV_1 in response to β_2-agonist, response to methacholine challenge, or presence of asthma as defined by the American Thoracic Society (37). Crossover trials were included if different interventions were administered in random order.

We decided a priori that inclusion criteria 3, 4, and 5 would be applied to trials of continued treatment. Studies of continued treatment were included if they did not report FEV_1 but instead evaluated the amount of β_2-agonist use and respiratory symptoms compared with placebo. Trials were also included if β_2-agonists were not withheld during the trial.

Assessment of Validity

The methodologic quality of each trial was assessed according to the following factors: 1) Was the study randomized? If so, was the randomization procedure adequate, and was allocation concealed? 2) Were the patients and people administering the treatment blinded to the intervention? 3) Were withdrawals and dropouts described, and was the analysis performed on an intention-to-treat basis? On the basis of these criteria, studies were broadly subdivided as all quality criteria met (A), one or more quality criteria only partially met (B), or one or more criteria not met (C).

Clinical trials that did not meet criteria for inclusion but gave information on FEV_1 response to cardioselective β-blockers in patients with reactive airway disease were analyzed separately and used in a sensitivity analysis. These included studies that were not placebo-controlled; did not document asthma criteria; did not give baseline FEV_1 data; or, for single-dose studies, did not withhold β_2-agonists for 8 hours before measurements.

Study Characteristics

The main intervention of interest was intravenous or oral cardioselective β-blockers versus placebo, given as a single dose or as continued treatment. Administration of a β_2-agonist, intravenously or by inhalation, after the study medication or after placebo was also studied.

Each β_1-blocker used was classified into one of two categories: β_1-blockers without intrinsic sympathomimetic activity, and β_1-blockers with intrinsic sympathomimetic activity.

Data Extraction

Two investigators independently extracted data on change in mean group FEV_1 in response to placebo or study drug; response of FEV_1 to β_2-agonist administered after placebo or study drug; symptoms reported during the trial, such as wheezing, dyspnea, or exacerbation of asthma; and, for trials of continued treatment, weekly use of inhaled short-acting β_2-agonists.

Data Synthesis

The ratio of the lowest group FEV_1 value after administration of study drug to baseline FEV_1 was measured for placebo and active treatment and was recorded as the percentage change from baseline. The placebo response was then subtracted from the treatment response to obtain the net treatment effect, reported as a percentage of the baseline FEV_1 value. For response to β_2-agonists given after treatment or placebo, the new baseline value was the mean group FEV_1 value obtained after study drug but before β_2-agonist administration. The net treatment effect was estimated by calculating the ratio of FEV_1 measured after agonist administration to the new baseline value for both placebo and active treatment and then subtracting the placebo–agonist response from the treatment–agonist response.

Whenever possible, the SD for the net treatment effect was calculated from individual-patient data or *P* values and was then used to derive the SDs for the analysis. Some trials provided SDs for treatment response and placebo response separately. For trials that reported no information on SDs, the average SD was obtained from trials that provided such data, calculated separately for placebo, treatment, and β-agonist responses. Sensitivity analyses were performed to evaluate the effect of including these trials by using the lowest and highest available SD in place of the pooled SD and also by excluding these trials from the analysis. The **Appendix Table** (available at www.annals.org) shows the method used to obtain SDs for each trial.

The mean treatment effects were pooled to obtain a weighted average of the study means using the fixed-effects model for continuous outcomes (38, 39). Confidence intervals with 95% significance were obtained for the pooled study means. The analysis was performed by using Meta View 4.1 (Cochrane Library software [Update Software, Oxford, United Kingdom]).

Results for respiratory symptoms were measured as a risk difference by subtracting the percentage of patients with respiratory events during treatment from the percentage of patients with respiratory events during placebo use. The risk differences were then pooled by using the fixed-effects model for dichotomous outcomes. The results for inhaler use during continued treatment trials were measured as the incidence of use during placebo minus the incidence of use during treatment. The weighted mean treatment effects were pooled by using the fixed-effects model for continuous outcomes.

To test for interstudy heterogeneity, the chi-square value was calculated for the assumption of homogeneity. In addition, the confidence intervals from the fixed-effects model were compared with those from the random-effects model (40). The fixed-effects model was chosen to report the results because minimal heterogeneity was seen in most of the analyses. When heterogeneity was noted, the results from both the random-effects model and fixed-effects model were reported.

A subgroup analysis was performed to compare the treatment effects of cardioselective β-blockers with and without intrinsic sympathomimetic activity. Another analysis was done to evaluate the response of patients with concomitant chronic airways obstruction, defined as a baseline FEV_1 of less than 80% of the normal predicted value or less than 1.8 L, or defined by using American Thoracic Society criteria (41). A third subgroup analysis evaluated the treatment response in participants known to have comorbid cardiovascular conditions, such as hypertension.

Data Synthesis

Search Results

The **Appendix Figure** (available at www.annals.org) shows the results of the search for articles. The database search identified 200 potentially relevant articles. After review of articles and bibliographies, 104 trials of β-blockers in patients with reactive airway disease were found. Of these trials, 29 met inclusion criteria: Nineteen gave information on singe-dose studies (42–60) and 10 provided data on continued treatment of longer duration (28, 51, 61–68). One of the articles (51) gave data for both types of administration. Interrater agreement for study eligibility was 94%. Consensus was reached on the remaining trials. The **Appendix Table** (available at www.annals.org) shows the characteristics of the included studies.

Clinical trials that did not meet inclusion criteria but gave data on FEV_1 responses to cardioselective β-blockers in patients with reactive airway disease were analyzed separately and used in a sensitivity analysis (69–78).

Methodologic Quality of Included Studies

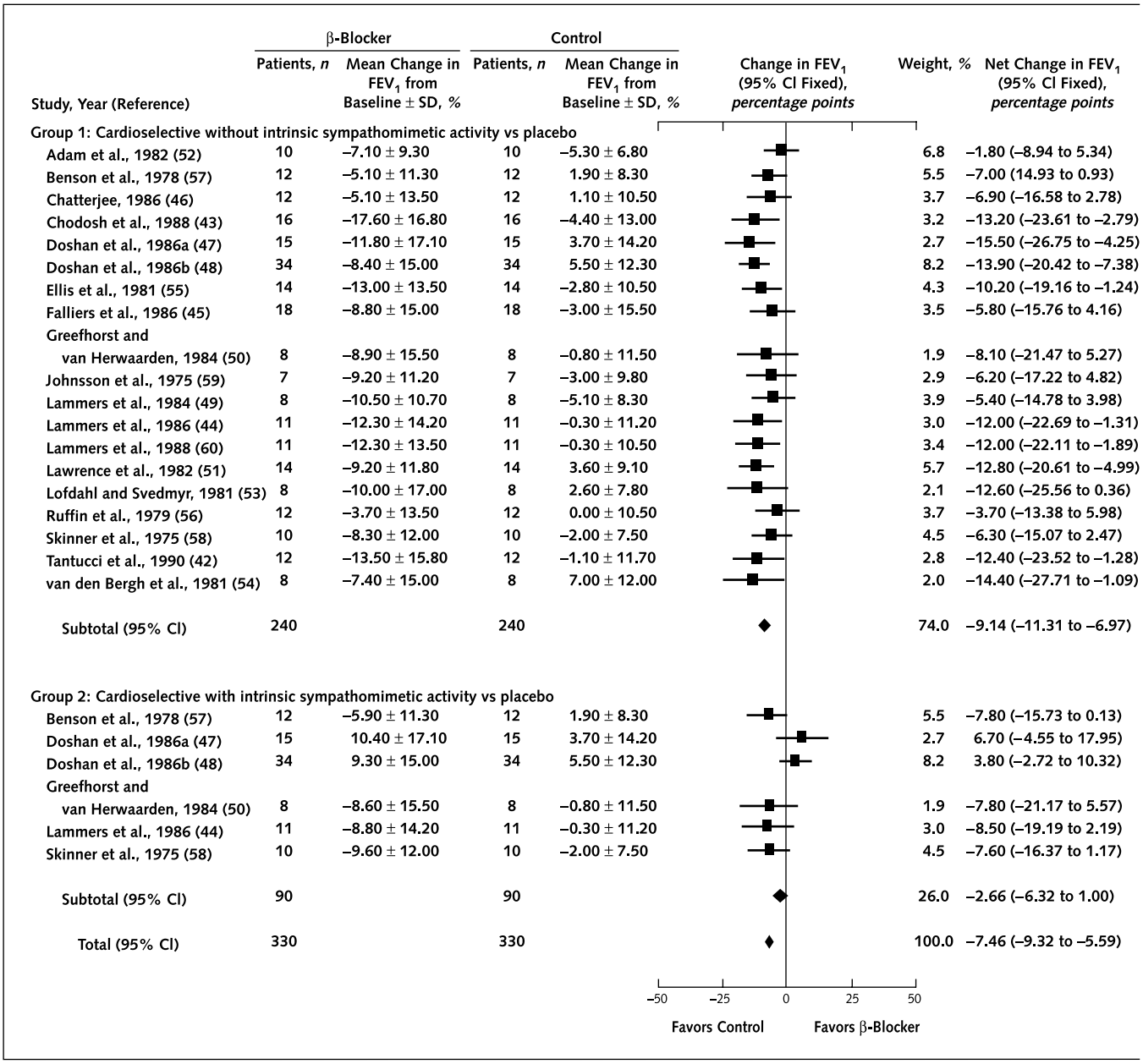
All studies were small crossover trials that received a quality score of B because the randomization process was not described in detail or the trial was single-blind instead of double-blind. Many of the trials were performed 20 or 30 years ago and did not provide adequate information with which to calculate SDs for the net treatment effect. Sensitivity analyses were performed to evaluate the effect of including trials that provided no information on SDs.

Quantitative Data Synthesis

Single-Dose Treatment

Nineteen studies of single-dose treatment included 240 patients, 79% of whom were men. Each study included an average of 12.6 patients, and the total dropout rate was 2.0%. From the available information, the age range of participants was 19.5 to 65.1 years (mean, 40.1 years). These baseline characteristics were the same for the placebo and treatment groups. The baseline FEV_1 was 2.41 ± 0.15 L in the treatment group and 2.42 ± 0.2 L in the placebo group. Cardioselective β-blockers without intrinsic sympathomimetic activity that were included in the study were atenolol, metoprolol, bisoprolol, and practolol. Cardioselective β-blockers with intrinsic sympathomimetic

Figure 1. **Effects of treatment on FEV_1 for single-dose studies.**



Diamonds represent the extent of the confidence intervals. For group 1, test for heterogeneity, $P > 0.2$; test for overall effect, $P < 0.001$. For group 2, test for heterogeneity, $P = 0.05$; test for overall effect, $P = 0.15$. For both groups, test for heterogeneity, $P = 0.09$; test for overall effect, $P < 0.001$.

activity that were studied were celiprolol, acebutolol, and xamoterol.

Compared with placebo, single doses of cardioselective β-blockers as a group were associated with a 7.46% (CI, 5.59% to 9.32%) reduction in FEV_1 but with a 4.63% (CI, 2.47% to 6.78%) increase in FEV_1 after β-agonist was given (**Figures 1** and **2**). The number of patients with respiratory symptoms did not increase significantly in any of the 19 studies (0.01% [CI, −0.02% to 0.03%]).

Continued Treatment

Data from 10 studies involving 141 participants (77% of whom were men) were evaluated for response to continued treatment ranging from 3 days to 4 weeks. Each study contained an average of 15.4 patients, and the dropout rate was 1.3%. From the available information, the average age of the participants was 51.3 years. The average baseline FEV_1 was 1.81 ± 0.13 L for the treatment group and 1.81 ± 0.15 L for the placebo group. Five of the studies (54 participants) did not provide data on FEV_1; these studies were included in analyses of symptoms and inhaler use.

In the continued treatment trials, cardioselective β-blockers as a group did not significantly differ from placebo in terms of FEV_1 response (−0.42% [CI, −3.74% to 2.91%]), number of patients with symptoms (0.01% [CI,

−0.02% to 0.04%]), or incidence of inhaler use (−0.11% [CI, −6.75% to 6.54%]). Cardioselective β-blockers produced an 8.74% increase (CI, 1.96% to 15.52%) in FEV_1 compared with placebo after β-agonist was given (**Figures 3** and **4**).

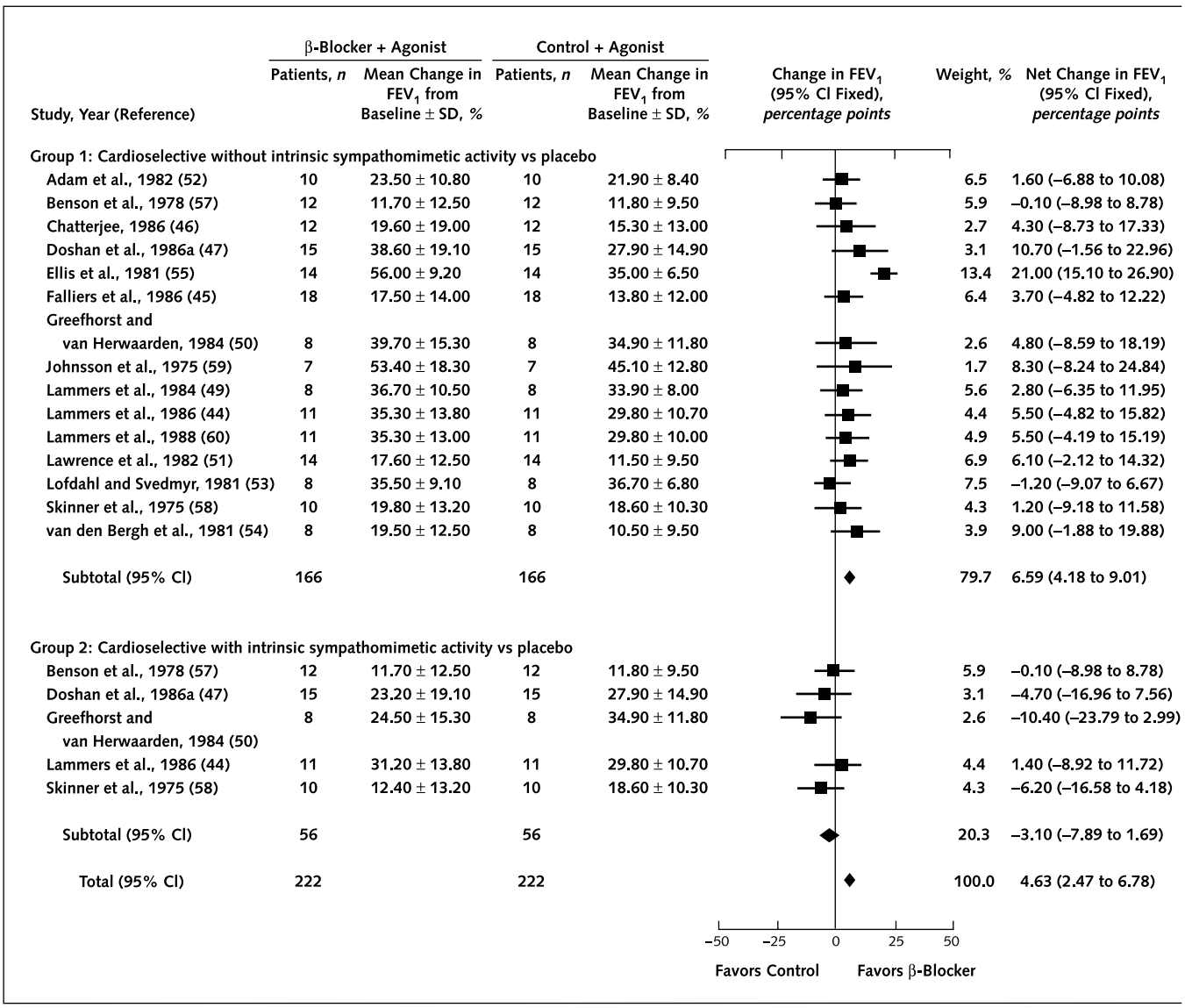
Interstudy Variance

No significant interstudy variance was found in FEV_1 treatment effect, symptoms, and long-term use of an inhaler. Heterogeneity was detected between studies in FEV_1 after β_2-agonist use in both the single-dose and continued treatment studies. This heterogeneity was noted only for β-blockers without intrinsic sympathomimetic activity. When the random-effects model was compared with the fixed-effects model for the β_2-agonist response in patients who received β-blockers without intrinsic sympathomimetic activity, a difference of less than 1 percentage point was found for single-dose studies (5.66% [CI, 1.81% to 9.51%] vs. 6.59% [CI, 4.18% to 9.01%]) and a difference of 1.7 percentage points was found for continued treatment studies (10.32% [CI, −6.38% to 27.01%] vs. 12.0% [CI, 4.12% to 19.89%]).

Subgroup Analysis

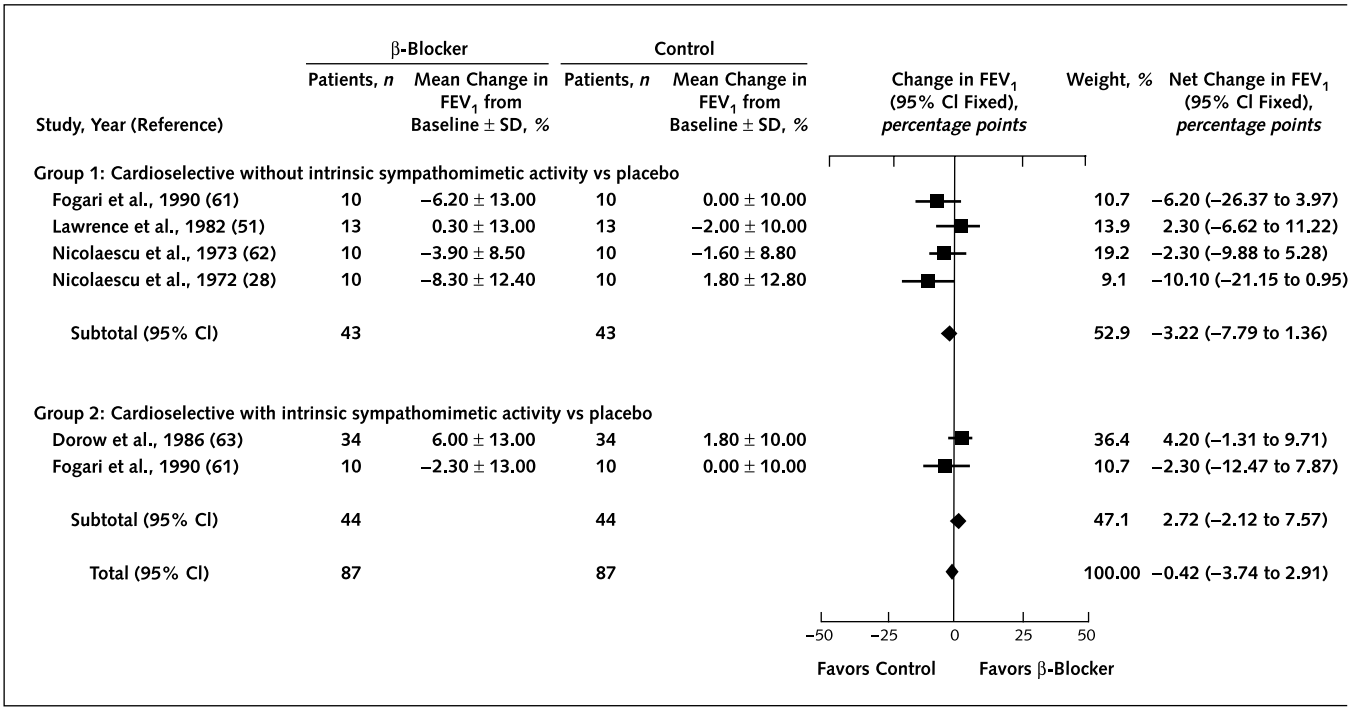
For single-dose trials, β_1-blockers without intrinsic sympathomimetic activity were associated with a 6.5% reduction in FEV_1 (CI, 2.2% to 10.7%) compared to those with sympathomimetic activity. However, treatment with β_1-blockers without intrinsic sympathomimetic activity was associated with a 9.7% increase in FEV_1 in response to β-agonist (CI, 5.6 to 13.7%) compared to those with sympathomimetic activity. In the continued treatment trials,

Figure 2. **Effects of treatment after use of β_2-agonists on FEV_1 for single-dose studies.**



Diamonds represent the extent of the confidence intervals. For group 1, test for heterogeneity, $P < 0.001$; test for overall effect, $P < 0.001$. For group 2, test for heterogeneity, $P > 0.2$; test for overall effect, $P = 0.2$. For both groups, test for heterogeneity, $P < 0.001$; test for overall effect, $P < 0.001$.

Figure 3. **Effects of treatment on FEV_1 for continued treatment studies.**



Diamonds represent the extent of the confidence intervals. For group 1, test for heterogeneity, $P > 0.2$; test for overall effect, $P = 0.17$. For group 2, test for overall effect, $P > 0.2$. For both groups, test for heterogeneity, $P = 0.18$; test for overall effect, $P > 0.2$.

no significant difference in FEV_1 response was observed for β_1-blockers without intrinsic sympathomimetic activity compared to those with sympathomimetic activity (5.94% [CI, −0.73% to 12.61%]). However, β-blockers without intrinsic sympathomimetic activity produced a 12.6% increase in FEV_1 (CI, 0.3% to 25.6%) after β-agonist administration compared to β-blockers with sympathomimetic activity.

To evaluate the treatment effect in patients with concomitant COPD, 10 trials that included only patients with documented chronic airway obstruction were analyzed separately (46, 52, 53, 59, 61, 63–66, 68). No significant difference in FEV_1 treatment effect was observed in single-dose trials (−5.28% [CI, −10.03% to −0.54%]) or continued treatment (1.07% [CI, −3.3% to 5.44%]), and no increase in symptoms occurred in any of the trials.

In eight of the trials, all participants had a comorbid condition, such as hypertension (46, 51, 52, 61, 63, 65, 67, 68). When only these trials were included in the analysis, the treatment effect for FEV_1 did not change significantly in single-dose trials (−6.83% [CI, −11.46% to −2.20%]) or with continued treatment (1.31% [CI, −2.62% to 5.24%]).

Sensitivity Analysis

A sensitivity analysis was performed to evaluate the effect of including studies that did not provide SDs (46, 55, 56, 60). When these trials were excluded from the analysis, the difference in all variables measured was less than 0.5 percentage point. When the analysis was performed by replacing the pooled SD with the lowest and highest available SD, the difference in results between the highest and lowest SD was 2 percentage points or less.

A sensitivity analysis was also performed to evaluate the effect of excluding trials that did not meet the inclusion criteria set by the study but that provided information on FEV_1 and symptoms for cardioselective β-blocker use in patients with reactive airway disease (69–78). Data analysis of 10 excluded studies with 141 participants showed no significant difference in any variables compared with studies that met inclusion criteria.

Discussion

Our results indicate that the first dose of a cardioselective β-blocker produces a small decrease in FEV_1 that is not associated with adverse respiratory effects compared to placebo. After continued treatment for a few days to weeks, FEV_1, symptoms, and inhaler use did not differ. Cardioselective β-blockers, given as a single dose or as continued treatment, were associated with an increase in response to β_2-agonists compared with placebo. Of the 80 trials on cardioselective β-blockers that we identified, none demonstrated an increase in respiratory symptoms for β_1-blockers compared with placebo or baseline values.

Subgroup analyses were performed to evaluate the effect of cardioselective β-blockers on patients with concom-

itant COPD or cardiovascular diseases, such as hypertension, because these patients are most often targeted for β-blocker treatment. No significant difference in the FEV_1 treatment effect or incidence of symptoms or inhaler use was observed.

Our meta-analysis has several limitations. Most of the participants were relatively young and had mild to moderate airway obstruction; persons with recent exacerbation of asthma were often excluded from study. In addition, because many of the studies were of short duration, we cannot comment on the effect of cardioselective β-blockers on the frequency or severity of acute asthma exacerbations after several months of treatment. Furthermore, this analysis was based only on published literature and therefore is subject to publication bias. However, funnel plots of effect size versus standard error for the trials in this analysis showed no evidence of bias. We believe that these pooled results provide valuable information on the safety of cardioselective β-blockers in patients with reactive airway disease, with or without concomitant COPD or cardiovascular disease.

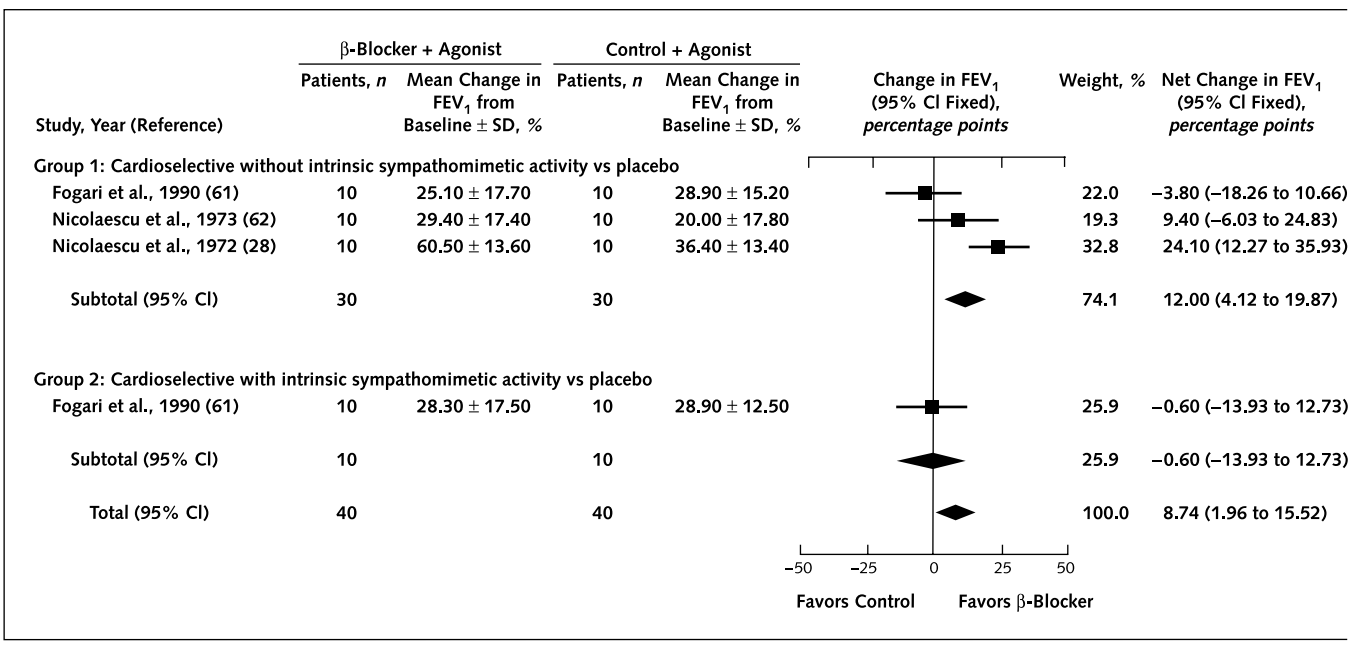
The current standard of care is to consider reactive airway disease to be a contraindication to the use of all β-blockers (6, 10, 18–22). Because of the proven mortality benefit of β-blockers, many of the other relative or absolute contraindications traditionally listed for β-blockers, including impaired left ventricular function, peripheral vascular disease, diabetes mellitus, depression, and advanced age (7, 14, 79–87), have been questioned and disproved.

The original evidence of a potential adverse effect of β-blockers in reactive airway disease was based on case reports of acute bronchospasm precipitated by high doses of noncardioselective blockers, presumably due to their blockade of β_2 receptors on bronchial smooth muscle (88–91). Pooled results of 16 trials that evaluated noncardioselective β-blockers showed that regular use of nonselective β-blockers compared with placebo caused a 13.5% decrease (CI, − 23.0% to −4.0%) in FEV_1 and a 22.5% decrease (CI, −32.5% to −12.5%) in the FEV_1 response after β_2-agonists were given (24, 32, 34, 43, 48, 52, 55–57, 59, 61, 68, 92–96). No significant increase in symptoms or inhaler use was found. However, the decrease in β-agonist response seen with nonselective β-blockers may increase the risk for a clinically significant adverse effect during an exacerbation of asthma.

Cardioselective β-blockers, such as atenolol, bisoprolol, and metoprolol, are at least 20 times more effective at blocking β_1-receptors than β_2-receptors; thus, at therapeutic doses, their β_2-blocking effect is negligible (23). The doses of β_1-blockers that we evaluated ranged from therapeutic to mildly supratherapeutic. For example, single-dose studies using atenolol or metoprolol in doses ranging from 50 to 200 mg showed no clinically apparent effect on respiratory function. Linear regression analysis could not differentiate a treatment effect between low and high doses because there were few low-dose trials and no trials used doses high enough to diminish cardioselectivity.

Our results indicate that for cardioselective β-blockers without intrinsic sympathomimetic activity, the minimal decrease in FEV_1 noted with a single dose is attenuated over a few days to weeks. In addition, FEV_1 increases in

Figure 4. **Effects of treatment after use of β_2-agonists on FEV_1 for continued treatment studies.**



Diamonds represent the extent of the confidence intervals. For group 1, test for heterogeneity, $P = 0.013$; test for overall effect, $P = 0.003$. For group 2, test for overall effect, $P > 0.2$. For both groups, test for heterogeneity, $P < 0.01$; test for overall effect, $P = 0.01$.

response to β_2-agonist administration compared with placebo, and this increase is maintained with continued treatment. These results could be explained by upregulation or sensitization of β_2 receptors that is accompanied by an increased effect of endogenous or exogenous β_2-agonist stimulation (97–99). Accumulating evidence indicates that continued use of inhaled β_2-agonists in patients with reactive airway disease is associated with a tolerance to β_2-agonist stimulation and an increase in asthma attacks (100–105). There is also evidence that treatment with β-blockers that have intrinsic β_2 sympathomimetic activity is associated with downregulation of β_2 receptors (106–109). This finding is consistent with data from our analysis showing that β-blockers with intrinsic sympathomimetic activity did not produce the increase in β_2-agonist response that was seen with β-blockers without intrinsic sympathomimetic activity.

Only a small proportion of patients with heart disease who would benefit from β-blockers currently receive this treatment, mainly owing to unfounded fears about their adverse effects (110–113). A study of survivors of myocardial infarction included 46 000 patients with asthma and chronic obstructive lung disease and showed a significant reduction in total mortality rate among those treated with β-blockers compared with those who were not (14). Other studies of the use of β-blockers in patients with cardiac disease and concomitant chronic obstructive lung disease or asthma found that these medicines were well tolerated (114–116). Other trials evaluating the use of β-blockers in hypertensive patients, many of whom had reactive airway disease, did not demonstrate worsening of respiratory symptoms or FEV_1 in these patients (32, 92, 117, 118). A recent study showed that COPD and asthma were the comorbid conditions most commonly associated with β-blockers' being withheld in elderly patients after a myocardial infarction (119).

Patients with COPD are thought to be at greater risk than those with reactive airway disease for developing ischemic heart disease and other cardiovascular conditions requiring the use of β-blockers. However, the presenting features of COPD and reactive airway disease overlap substantially.

Another recent meta-analysis evaluated the effect of cardioselective β-blockers in patients with COPD and found no change in FEV_1 or respiratory symptoms for single doses or continued use of these agents compared with placebo (25). Subgroup analyses revealed no difference in results for patients with concomitant reactive airway disease and those with severe chronic airways obstruction, as demonstrated by a baseline FEV_1 less than 1.4 L or less than 50% the normal predicted value. Three of the trials from that meta-analysis are also included in our analysis (52, 61, 66). The cumulative evidence from these two meta-analyses indicates that cardioselective β-blockers should not be withheld in patients with reactive airway disease or COPD.

From Stanford University School of Medicine, Palo Alto, California; Santa Clara Valley Medical Center, San Jose, California; and Cornell University, Ithaca, New York.

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Requests for Single Reprints: Shelley Salpeter, MD, Department of Medicine, Santa Clara Valley Medical Center, 751 South Bascom Avenue, San Jose, CA 95128; e-mail, shelley.salpeter@hhs.co.santa-clara.ca.us.

Current author addresses and author contributions are available at www.annals.org.

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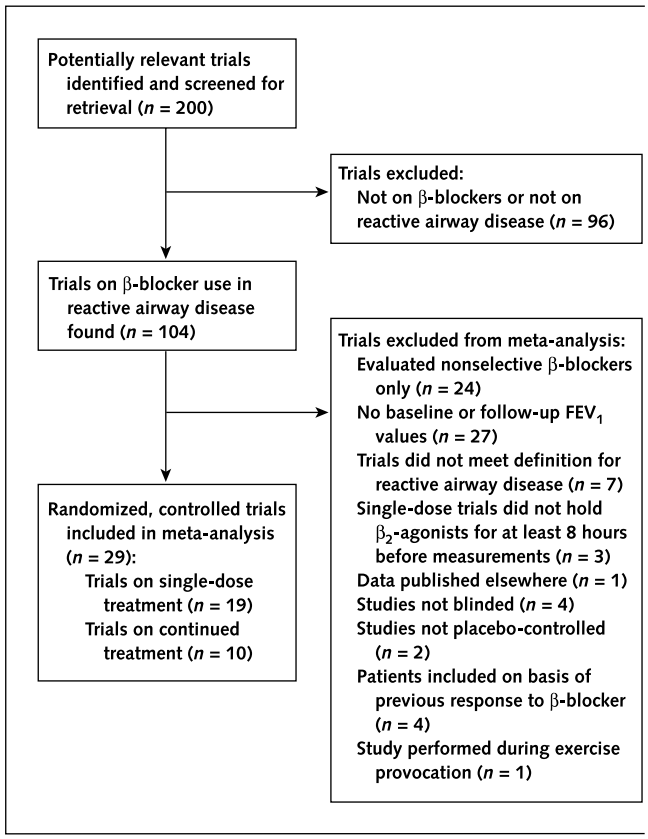
Current Author Addresses: Dr. S. Salpeter: Department of Medicine, Santa Clara Valley Medical Center, 751 South Bascom Avenue, San Jose, CA 95128.
Dr. Ormiston: Santa Clara Valley Medical Center, 751 South Bascom Avenue, San Jose, CA 95128.
Dr. E. Salpeter: Center for Radiophysics and Space Research, Cornell University, 612 Space Sciences Building, Ithaca, NY 14853.

Author Contributions: Conception and design: S.R. Salpeter, T.M. Ormiston.
Analysis and interpretation of the data: S.R. Salpeter, T.M. Ormiston, E.E. Salpeter.
Drafting of the article: S.R. Salpeter, T.M. Ormiston.
Critical revision of the article for important intellectual content: S.R. Salpeter, T.M. Ormiston.
Final approval of the article: S.R. Salpeter, T.M. Ormiston, E.E. Salpeter.
Provision of study materials or patients: S.R. Salpeter, T.M. Ormiston.
Statistical expertise: E.E. Salpeter.
Collection and assembly of data: S.R. Salpeter, T.M. Ormiston.

Appendix Figure. **Results of search for and selection of trials.**



Appendix Table. **Characteristics of Included Studies***

Study, Year (Reference)	Design	Inclusion and Exclusion Criteria†	Participants	Dropout Rate	Mean Age or Age Range
			n	%	*y*
Adam et al., 1982 (52)	Single dose, double-blind, crossover	Inclusion: hypertension and reversible airway disease	10	0	65.1
Bauer et al., 1994 (65)	Crossover (1 week treatment and 1 week placebo), double-blind	Inclusion: hypertension and stable asthma Exclusion: cardiac disease, renal disease, hepatic disease, diabetes, pregnancy, adverse reaction to β-blocker	18	0	48.6
Benson et al., 1978 (57)	Single dose, crossover, single-blind	Inclusion: reversible airway obstruction, stable	12	14 before start of study	32.2
Butland et al., 1983 (64)	Crossover (4 weeks treatment and 4 weeks placebo), double-blind	Inclusion: COPD, $FEV_1 < 1$ L with >20% reversal; inhalers, steroids allowed Exclusion: other lung disease or other serious disease	12	0	61
Chatterjee, 1986 (46)	Single dose, crossover, double-blind	Inclusion: asthma and hypertension, FEV_1/vital capacity < 30% Exclusion: pregnancy, heart or renal failure, antihypertensive or inhaler treatment	12	0	60
Chodosh et al., 1988 (43)	Single dose, crossover, double-blind	Inclusion: normotensive patients with stable asthma, FEV_1 60%–90% predicted Exclusion: cromolyn use; change in steroid or inhaler use; recent asthma attack, upper respiratory tract infection, or status asthmaticus	16	11 before start of study	39
Dorow et al., 1986 (63)	Crossover (12 weeks treatment, 4 weeks placebo), double-blind	Inclusion: hypertension and reversible airway obstruction Exclusion: severe hypertension	34	0	Unclear
Doshan 1986a (47)	Single dose, crossover, double-blind	Inclusion: mild asthma	15	6	19–55
Doshan et al., 1986 (48)	Single dose, crossover, double-blind	Inclusion: normotensive and asthma, $FEV_1 > 50\%$ predicted Exclusion: cromolyn or steroid use	34	0	18–57
Ellis et al., 1981 (55)	Single dose, crossover, double-blind	Inclusion: reversible airway disease	14	0	Unclear
Falliers et al., 1986 (45)	Single dose, crossover, double-blind	Inclusion: asthma, $FEV_1 < 80\%$ predicted Exclusion: hypertension, hematologic or cardiovascular disease, recent asthma attack or respiratory infection, status asthmaticus, or cromolyn therapy	18	0	21–60
Fenster et al., 1983 (66)	Crossover (1 week treatment, 1 week placebo), single-blind	Inclusion: reversible airway disease	6	0	48.6
Fogari et al., 1990 (61)	Crossover (1 week treatment, 2 weeks placebo), double-blind	Inclusion: hypertension and reversible airway disease Exclusion: cardiovascular disease, renal insufficiency	10	0	57
Greefhorst and van Herwaarden, 1984 (50)	Single dose, crossover, double-blind	Inclusion: intrinsic atopic asthma, stable Exclusion: cardiovascular disease	8	0	29
Johnsson et al., 1975 (59)	Single dose, crossover, single-blind	Inclusion: asthma for > 2 years Exclusion: acute exacerbation, heart disease	7	0	44
Lammers et al., 1984 (49)	Single dose, crossover, double-blind	Inclusion: asthma, some with chronic bronchitis Exclusion: recent respiratory tract infection or increase in bronchoconstriction	8	0	39
Lammers et al., 1985 (68)	Crossover (4 weeks treatment and placebo), double-blind	Inclusion: COPD and hypertension, with average FEV_1 reversal > 15%; all stable, with no recent respiratory tract infection or event Exclusion: none listed	8	0	52.7
Lammers et al., 1986 (44)	Single dose, crossover, single- and double-blind	Inclusion: asthma Exclusion: heart disease	11	0	6.6
Lammers et al., 1988 (60)	Single dose, crossover, single-blind	Inclusion: asthma, FEV_1 40%–74% predicted, stable without steroids or theophylline Exclusion: none listed	11	0	22–60
Lawrence et al., 1982 (51)	Crossover (single dose, then 3 weeks treatment and placebo), single-blind	Inclusion: asthma and hypertension	14	0	55.7
Lofdahl et al., 1981 (53)	Single dose, crossover, double-blind	Inclusion: intrinsic asthma, stable Exclusion: none listed	8	0	52
Nicolaescu et al., 1973 (62)	Crossover (3 days treatment and 3 days placebo), double-blind	Inclusion: severe asthma for > 5 years; steroids continued, inhalers held before measurements Exclusions: recent asthma attack	10	0	46.6
Nicolescu et al., 1972 (28)	Crossover (3 days treatment and 3 days placebo)	Inclusion: mild asthma for > 5 y Exclusion: none listed	10	0	43.7
Ruffin et al., 1979 (56)	Single dose, crossover, double-blind	Inclusion: asthma with episodic dyspnea Exclusion: $FEV_1 < 70\%$ predicted, or symptoms out of control	12	0	30.8
Skinner et al., 1975 (58)	Single dose, crossover, double-blind	Inclusion: asthma	10	0	36.8
Tantucci et al., 1990 (42)	Single dose, crossover, double-blind	Inclusion: reversible airway disease, stable Exclusion: history of atopy, recent respiratory tract infection, contraindications to β-blocker, pregnancy	12	0	37.3
van den Bergh and van Herwaarden, 1981 (54)	Single dose, crossover, single- and double-blind	Inclusion: asthma, mild to moderate, stable	8	0	24
van Zyl et al., 1989 (67)	Crossover (4 weeks treatment, 2 weeks placebo), single- and double-blind	Inclusion: asthma and hypertension, $FEV_1 < 85\%$ predicted	12	16	45.9

* COPD = chronic obstructive pulmonary disease; OT = ordinary tablets; SR = sustained release.
† Some studies did not list exclusion criteria.

Appendix Table—**Continued**

Active Interventions	Comparison Interventions	Outcomes Measured	Comments
1: metoprolol, 100 mg; atenolol, 100 mg 2: inhaled salbutamol after treatment	1: placebo 2: inhaled salbutamol after placebo	FEV_1, symptoms	Nonselective agents studied were labetalol and propranolol; SDs derived from individual-patient data or *P* values
Osmotic-release metoprolol, 204 mg/d, atenolol, 100 mg/d	Placebo	Symptoms	
1: acebutolol, 300 mg; atenolol, 100 mg 2: inhaled isoprenaline after treatment	1: placebo 2: inhaled isoprenaline after placebo	FEV_1, symptoms	Nonselective agents studied were propranolol and pindolol; SDs derived from individual-patient data or *P* values
Atenolol, 100 mg/d; metoprolol, 100 mg/d	Placebo	Symptoms, exercise tolerance	FEV_1 reported as percentage of predicted normal value
1: atenolol, 100 mg; bisoprolol, 10 mg; bisoprolol, 20 mg 2: inhaled salbutamol after treatment	1: placebo 2: inhaled isoprenaline after placebo Atenolol, 100 mg/d; metoprolol, 100 mg/d	FEV_1 symptoms	No SDs provided 2
1: metoprolol 200 mg 2: inhaled isoproterenol after treatment	1: placebo 2: inhaled isoproterenol after placebo	FEV_1 symptoms	Nonselective agent studied was dilevalol; SDs derived from individual patient data or *P* values
Celiprolol, 100–600 mg/d	Placebo	FEV_1, symptoms, weekly inhaler use	SDs were reported for treatment effect and placebo effect separately
1: celiprolol, 400 mg; celiprolol, 600 mg; atenolol, 100 mg 2: inhaled albuterol after treatment	1: placebo 2: inhaled albuterol after placebo	FEV_1, symptoms	SDs were reported for treatment effect and placebo effect separately
Celiprolol, 200 mg; celiprolol, 400 mg; atenolol, 100 mg	Placebo	FEV_1, symptoms	Nonselective agent studied was propranolol; SDs were reported for treatment effect and placebo effect separately
1: atenolol, 50 mg; atenolol, 100 mg; atenolol, 200 mg 2: inhaled isoprenaline after treatment	1: placebo 2: inhaled isoprenaline after placebo	FEV_1, symptoms	Nonselective agent studied was propranolol; no SD data provided
1: metoprolol, 100 mg; metoprolol, 200 mg 2: inhaled isoproterenol after treatment	1: placebo 2: inhaled isoproterenol after placebo	FEV_1, symptoms	Nonselective agent studied was labetalol; SDs were reported for treatment effect and placebo effect separately
Metoprolol, 200 mg/d	Placebo	Increase in symptoms	FEV_1 reported as percentage of predicted value
1: atenolol, 100 mg/d; celiprolol 200 mg/d 2: inhaled salbutamol after treatment	1: placebo 2: inhaled salbutamol after placebo	FEV_1, symptoms	Nonselective agents studied were propranolol and oxprenolol; SDs were reported for treatment effect and placebo effect separately
1: metoprolol, 100 mg; acebutolol, 400 mg 2: intravenous terbutaline after treatment	1: placebo 2: intravenous terbutaline after placebo	FEV_1, symptoms	SDs were reported for treatment effect and placebo effect separately
Intravenous metoprolol, 0.12 mg/kg body weight	Intravenous placebo	FEV_1, symptoms	Isoprenaline given intravenously, but FEV_1 not reported; nonselective agent studied was propranolol; SDs derived from individual-patient data or *P* values
1: bisoprolol, 10 mg; bisoprolol, 20 mg; metoprolol, 100 mg 2: inhaled terbutaline after treatment	1: placebo 2: inhaled terbutaline after placebo	FEV_1, symptoms	SDs were reported for treatment effect and placebo effect separately
Metoprolol, 100 mg twice daily	Placebo	Symptoms	Nonselective agent studied was pindolol
1: xamoterol, 200 mg; atenolol, 100 mg 2: inhaled terbutaline after treatment	1: placebo 2: inhaled terbutaline after placebo	FEV_1, symptoms	Placebo given single-blind, treatments given double-blind; SDs were reported for treatment effect and placebo effect separately
1: atenolol, 50 mg 2: inhaled terbutaline after treatment	1: placebo 2: inhaled terbutaline after placebo	FEV_1, symptoms	No SDs provided
1: atenolol, 100 mg; metoprolol, 100 mg 2: inhaled salbutamol after treatment 3: atenolol, 100 mg/d; metoprolol, 100 mg twice daily	1: placebo 2: inhaled salbutamol after placebo 3: placebo	FEV_1, symptoms, asthma attacks, weekly inhaler use	SDs derived from individual-patient data or *P* values
1: atenolol, 100 mg; metoprolol 100 mg 2: terbutaline, intravenous then inhaled, after treatment	1: placebo 2: terbutaline, intravenous then inhaled, after placebo	FEV_1, symptoms	SDs derived from individual-patient data or *P* values
1: practolol, 200 mg/d 2: inhaled orciprenaline after treatment	1: placebo 2: inhaled orciprenaline after placebo	FEV_1, symptoms	SDs derived from individual-patient data or *P* values
1: practolol, 50 mg four times daily 2: inhaled orciprenaline after treatment	1: placebo 2: inhaled orciprenaline after placebo	FEV_1, symptoms	SDs derived from individual-patient data or *P* values
Metoprolol, 100 mg	Placebo	FEV_1, symptoms	Nonselective agents studied were propranolol and timolol; no SDs provided
1: acebutolol, 300 mg; practolol, 300 mg 2: inhaled isoprenaline after treatment	1: placebo 2: inhaled isoprenaline after placebo	FEV_1, symptoms	SDs were reported for treatment effect and placebo effect separately
Osmotic-release metoprolol, 204 mg; atenolol, 100 mg	Placebo	FEV_1, symptoms	SDs derived from individual-patient data or *P* values
1: metoprolol OT, 100 mg; metoprolol OT, 200 mg; metoprolol SR, 200 mg 2: intravenous terbutaline after treatment	1: placebo 2: intravenous terbutaline after placebo	FEV_1, symptoms	Single-blind; metoprolol, 100 mg, and placebo; double-blind: metoprolol, 200 mg, 2 doses; SDs derived from individual-patient data or *P* values
Atenolol, 100 mg/d; celiprolol, 400/d	Placebo	Symptoms, weekly inhaler use	Placebo run-in, single-blind; treatment double-blind