

Cardioselective beta-blockers for chronic obstructive pulmonary disease (Review)

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ABSTRACT

Background

Beta-blocker therapy has a proven mortality benefit in patients with hypertension, heart failure and coronary artery disease, as well as during the perioperative period. These drugs have traditionally been considered contraindicated in patients with chronic obstructive pulmonary disease (COPD).

Objectives

To assess the effect of cardioselective beta-blockers on respiratory function of patients with COPD.

Search strategy

A comprehensive search of the Cochrane Airways Group Specialised Register (derived from systematic searches of CENTRAL, MEDLINE, EMBASE and CINAHL) was carried out to identify randomised blinded controlled trials from 1966 to May 2005. We did not exclude trials on the basis of language.

Selection criteria

Randomised, blinded, controlled trials of single dose or longer duration that studied the effects of cardioselective beta-blockers on the forced expiratory volume in 1 second (FEV1) or symptoms in patients with COPD.

Data collection and analysis

Two independent reviewers extracted data from the selected articles, reconciling differences by consensus. Two interventions studied were the administration of beta-blocker, given either as a single dose or for longer duration, and the use of beta2-agonist given after the study drug.

Main results

Eleven studies of single-dose treatment and 9 of treatment for longer durations, ranging from 2 days to 12 weeks, met selection criteria. Cardioselective beta-blockers, given as a single dose or for longer duration, produced no change in FEV1 or respiratory symptoms compared to placebo, and did not affect the FEV1 treatment response to beta2-agonists. A subgroup analysis revealed no change in results for those participants with severe chronic airways obstruction or for those with a reversible obstructive component.

Authors' conclusions

Cardioselective beta-blockers, given to patients with COPD in the identified studies did not produce adverse respiratory effects. Given their demonstrated benefit in conditions such as heart failure, coronary artery disease and hypertension, cardioselective beta-blockers should not be routinely withheld from patients with COPD.

PLAIN LANGUAGE SUMMARY

Long term treatment with beta-blocker medication reduces the risk of death in patients with hypertension, heart failure and coronary artery disease, yet patients with COPD in addition to their cardiovascular disease seldom receive these medicines because of fears that

they may worsen the airways disease. This review of data from 20 randomised controlled trials on the use of cardioselective beta-blockers in patients with COPD demonstrated no adverse effect on lung function or respiratory symptoms compared to placebo. This finding was consistent whether patients had severe airways chronic airways obstruction or a reversible obstructive component. In conclusion, cardioselective beta-blockers should not be withheld from patients with COPD.

BACKGROUND

Beta-adrenergic blocking agents, or beta-blockers, are indicated in the management of angina pectoris, myocardial infarction, hypertension, congestive heart failure, cardiac arrhythmia and thyrotoxicosis, as well as to reduce complications in the peri-operative period (Doughty 1997; Freemantle 1999; Heidenreich 1999; IPPSH 1985; JNC 1997; Jones 1980; Kendall 1997; Klein 1994; Koch-Weser 1984; Lechat 1998; Mangano 1996; Steinbeck 1992; Wadworth 1991). Despite clear evidence of their effectiveness and mortality benefit, clinicians are often hesitant to administer them in the presence of a variety of common conditions for fear of adverse reactions (Gottlieb 1998; Kennedy 1995; Viskin 1996; Chafin 1999). Review articles and practice guidelines usually list asthma and chronic obstructive pulmonary disease (COPD) as contraindications to beta-blocker use, citing cases of acute bronchospasm occurring during non-cardioselective beta-blocker use (JNC 1997; Kendall 1997; Craig 1996; Belli 1995; O'Malley 1991; Tattersfield 1986; Tattersfield 1990). Cardioselective beta-blockers, or beta₁-blockers, have over 20 times more affinity for beta-1 receptors as for beta-2 receptors, and theoretically should have significantly less risk for bronchoconstriction (Wellstein 1987).

A recent Cochrane review demonstrated that cardioselective beta₁-blockers, given to patients with mild to moderate reversible airway disease, do not produce clinically significant adverse respiratory effects (Salpeter 2001). The study was not designed to make recommendations about people with significant chronic airway obstruction because only a few COPD patients met the reversibility criteria for the study. Patients with COPD are at greater risk of ischemic heart disease than asthmatics, so would benefit from the use of beta-blockers. However, they also have more severe airways obstruction, so may be more sensitive to small changes in FEV₁ due to beta-blockade.

OBJECTIVES

To evaluate the effect of cardioselective beta₁-blockers on respiratory function in patients with COPD, as assessed by FEV₁ and the incidence of symptoms. Another objective was to evaluate the FEV₁ response to beta₂-agonists for those patients treated with beta₁-blockers as compared to placebo.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

A search was performed to identify all relevant published clinical trials that address the effects of cardioselective beta-blockers on airway function in patients with COPD. Trials were included if they: (1) reported FEV₁ measured at rest, either as litres or as a percent of the normal predicted value at baseline and follow-up, or reported symptoms for study drug and placebo, (2) were randomised, controlled, and single or double-blinded, and (3) included only subjects with COPD, demonstrated by a baseline FEV₁ of < 80% normal predicted value, or as defined by the guidelines of the American Thoracic Society (ATS 1995). Cross-over trials were considered to be randomised if different interventions were administered in random order. Controlled trials were those with placebo or comparative controls.

The decision was made to evaluate only cardioselective beta₁-blockers in this study as these are the ones most frequently used in clinical practice. Studies were included only if participants had documented COPD, in order to evaluate the effect of cardioselective beta-blockers in patients with chronic airway obstruction. Only blinded studies were included in order to decrease the risk of reporting bias that is inherent in unblinded studies. It was decided a priori to data extraction that comparative trials studying FEV₁ treatment effects of cardioselective beta-blockers without placebo controls would be included as long as they compared various interventions in a blinded randomised manner. Sensitivity analysis was performed to evaluate the effect of including these studies. For studies that evaluated symptoms, only those that have placebo controls for comparison to active treatment were included.

Types of participants

Participants studied were those with COPD, defined as a disease state with chronic airway obstruction according to the guidelines of the ATS (ATS 1995), or with a baseline FEV₁ of less than 80% normal predicted value. Participants were not included or excluded on the basis of reversibility of their airway obstruction.

Types of intervention

The main intervention studied was the use of intravenous or oral cardioselective beta-blockers versus placebo or other interventions, given either as a single dose or for an extended period. A second intervention studied was the administration of a beta₂-agonist,

either intravenously or by inhalation, given after the study medication or placebo. For single-dose trials the beta-agonist was given one hour after the administration of an intravenous agent, and 3 to 6 hours after an oral agent was given.

Types of outcome measures

Two investigators (SS, TO) independently extracted data on three outcomes: (1) the change in FEV1 from baseline in response to study group or placebo, (2) FEV1 response to beta2-agonist administered after placebo or study drug, and (3) reported symptoms during the trial, such as wheezing, dyspnea, or COPD exacerbation, for study drug or placebo.

For single-dose trials of oral medications the FEV1 measurement were recorded from one to six hours after drug administration, with all trials measuring FEV1 at least 3 hours after treatment was given. When intravenous medications were used, the FEV1 was measured repeatedly for one hour after the treatment was given. For trials using beta2-agonists, FEV1 measurements were taken 10 minutes after intravenous beta-agonist and 20-30 minutes after inhalation of the agent.

Respiratory symptoms were measured according to a self-reporting system used for each trial, and were reported as the number of patients with symptoms. For single-dose trials respiratory symptoms were described as wheezing, dyspnea or breathlessness. For trials of longer duration patients were to record symptoms such as acute shortness of breath, increased respiratory symptoms, asthma attacks or COPD exacerbations.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Airways Group methods used in reviews.

Two investigators (SS, TO) jointly developed strategies, with the help of an information service librarian and the Cochrane Airways Group Trial Search Co-ordinator. A search was performed using the Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Airways Group Specialised Register to identify blinded controlled trials on chronic obstructive pulmonary disease. The Specialised Register is derived from systematic searches of bibliographic databases including CENTRAL, MEDLINE, EMBASE and CINAHL, and hand-searching of respiratory journals and meeting abstracts. All records in the Specialised Register coded as 'COPD' were searched using the following terms:

(adrenergic* and antagonist*) or (adrenergic* and block*) or (adrenergic* and beta-receptor*) or (beta-adrenergic* and block*) or (beta-blocker* and adrenergic*) or (blockader* or Acebutolol or Alprenolol or Atenolol or Betaxolol or Bisoprolol or Bupranolol or Butoxamine or Carteolol or Celiprolol or Dihydroalprenolol or Iodocyanopindolol or Labetalol or

Levobunolol or Metipranolol or Metoprolol or Nadolol or Oxprenolol or Penbutolol or Pindolol or Practolol or Propranolol or Sotalol or Timolol)

This search was adapted for use in CENTRAL and combined with the Airways Group 'COPD' search.

Trials were not excluded on the basis of language. The search was further augmented by scanning references of identified articles or reviews, and of abstracts at clinical symposia. The current overview includes a search update to May 2005.

METHODS OF THE REVIEW

Two investigators (SS, TO) independently evaluated studies for inclusion and the observed percentage agreement between raters was calculated. Studies were evaluated if they gave intravenous or oral cardioselective beta-blockers, either as a single dose or for an extended period. Two independent reviewers (SS, TO) extracted data from the selected articles, reconciling differences by consensus. Only published data from the trials were included in the analysis. No attempts were made to contact the original authors to verify the data or obtain more information, as all of the trials were small and published several years ago. Data from single-dose trials and those of longer duration were analysed separately.

The baseline FEV1 used for single-dose trials was that measured on the study day prior to the administration of study drug. For longer-duration trials baseline FEV1 measurements were taken prior to the initiation of treatment. For all trials in which more than one FEV1 measurement was reported after administration of the study drug the lowest FEV1 was used for the analysis.

To estimate the net treatment effect, the ratio of the lowest measured FEV1 value seen after study drug to baseline FEV1 were measured for both placebo and active treatment, and recorded as the percent change from baseline. The treatment response was then compared to the placebo response. For those studies without placebo controls (see Table of Included Studies) the treatment response for each intervention was measured and the placebo response was estimated from the available placebo-controlled trials. Sensitivity analysis was performed to evaluate the effect of including these trials.

For those trials that did not report the standard deviation for the distribution of study results (SD), the average SD was obtained from the available information and calculated separately for placebo and treatment responses. This pooled SD was used for all trials that did not provide SD data (see Table of Included Studies). 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 mean treatment effects were then pooled to get a weighted average of the study means using a fixed-effects model for continuous outcomes (Mantel-Haenszel method) (Mantel 1959; Yusuf 1985). Confidence intervals (CI) with 95% significance were obtained for the pooled study means. In order to test for heterogeneity between studies, the chi-squared was calculated for the assumption of homogeneity.

In order to evaluate the response to beta2-agonist given after active treatment or placebo, the new baseline used was the FEV1 taken after study drug but prior to beta-agonist. The net treatment effect was estimated by calculating the ratio of FEV1 measured after agonist to the new baseline for both placebo and active treatment, and then comparing the treatment-agonist response to the placebo-agonist response.

Results for respiratory symptoms were measured as a risk difference, by subtracting the number of participants with symptoms in the placebo group from the number of those with symptoms in the treatment group. The risk differences were then pooled using the fixed effects model for dichotomous outcomes.

A subgroup analysis was performed to evaluate the response of patients with severe COPD, as defined by a mean baseline FEV1, for the group, of less than 1.4 litres or less than 50% normal predicted value. Another subgroup analysis evaluated the treatment response of participants known to have reversible airway obstruction, documented by an increase in FEV1 of at least 15% to beta-agonist stimulation. A third analysis evaluated the response for those known to have comorbid cardiovascular conditions such as hypertension or angina.

DESCRIPTION OF STUDIES

The database search identified 235 potentially relevant articles. After review of the articles and bibliographies, 40 trials of beta-blockers in patients with COPD were found. Of these, 20 met inclusion criteria: 11 gave information on single-dose studies (Adam 1982; Anderson 1980; Sinclair 1979; Beil 1977; von Wichert 1982; Dorow 1986b; Schanning 1976; Macquin-Mavier 1988; Perks 1978; Sorbini 1982; McGavin 1978), and 9 provided data on treatment of longer duration (Butland 1983; Wunderlich 1980; Tivenius 1976; Lammers 1985a; Butland 1983; Dorow 1986a; Fenster 1983; Ranchod 1982; Fogari 1990; van der Woude 2005). Inter-rater agreement for study eligibility was 94%. Of the single-dose trials, 4 provided appropriate FEV1 data and 9 provided placebo controls for symptom analysis. Of the trials of longer duration, 5 were used for FEV1 analysis and 8 for symptoms. The FEV1 response to beta2-agonists were recorded in 2 single-dose trials (Adam 1982; Sinclair 1979) and in 2 longer duration trial (Fogari 1990; van der Woude 2005).

Trials were excluded for the following reasons: 8 trials evaluated nonselective beta-blockers only (Addis 1976; Wettengel 1970; Ul-

mer 1976; Nordstrom 1975; Meier 1966a; Anavekar 1982; Chester 1981; George 1983), 1 study was a duplicate trial (Meier 1966b), 2 studies were not randomised (Quan 1983; Abraham 1981), 4 were not blinded (Dorow 1984; Dorow 1986c; Dal Negro 1986; Dal Negro 1981), 1 did not provide FEV1 data or placebo-controls (Clague 1984), and 4 were reviews of other trials (Johnsson 1976; van Herwaarden 1983; Lois 1997; Lois 1999).

METHODOLOGICAL QUALITY

All of the studies evaluated were small cross-over trials that included a wash-out period between treatment groups. Many were performed 20 or 30 years ago, and the randomisation process was not described in detail. Some of the trials were single-blind instead of double-blind. Many of the trials did not have placebo controls or provide individual study SDs for the FEV1 treatment effect, and 1 study merely evaluated different doses of a single drug compared to baseline controls. Sensitivity analyses were performed to evaluate the effect of including these trials.

RESULTS

Cardioselective beta-blockers included in the study were atenolol, metoprolol, bisoprolol, practolol, celiprolol and acebutolol.

Single-Dose Treatment Results:

Eleven studies on single-dose treatment included 131 patients, 80% of whom were men. There was an average of 11.9 patients per study, and the dropout rate was 1.5%. From the available information the mean age of participants was 53.8 (+/- 11.1) years. These baseline characteristics were the same for the placebo and treatment groups because all of the trials were crossover by design. The baseline FEV1 measured in the treatment group was 1.64 (+/- 0.63) litres, and in the placebo group was 1.66 (+/- 0.64) litres.

Single doses of cardioselective beta-blockers were not associated with a change in FEV1 compared to placebo or to baseline controls with a weighted mean difference (WMD) of -2.08% (95% CI, -5.25 to 1.09). No increase in respiratory symptoms were seen for beta1-blockers compared to placebo in any of the trials, with a risk difference (RD) of 0.0% (95% CI, -0.04 to 0.04). In the 2 trials that measured response to inhaled beta2-agonist after treatment and after placebo (Adam 1982; Sinclair 1979), there was no significant change in the net treatment effect (WMD -1.21% [95% CI, -10.97 to 8.56]).

Longer Duration Treatment Results:

Data from 9 studies involving 147 participants and 998 patient-weeks were evaluated for treatment effects of longer duration ranging from 2 days to 12 weeks, with a mean trial duration of 3.7 weeks. There was an average of 16.3 participants in each study (78% of whom were men), with a 3.4% dropout rate. The average

baseline FEV1 in the treatment group was 1.81 (+/- 0.72) litres, and for the placebo group was 1.80 (+/- 0.73) litres..

When cardioselective beta-blockers were compared to placebo, there was no significant change in FEV1 treatment effect (WMD -2.39% [95%CI, -5.69 to 0.91]) or respiratory symptoms (RD 0.0% [95%CI, -0.05 to 0.05]). In the two trials that measured FEV1 response to inhaled beta2-agonist after treatment and placebo (Fogari 1990; van der Woude 2005), there was no significant difference in the net treatment effect after treatment compared to placebo (WMD 1.12% [95%CI, -4.97 to 7.20]).

Interstudy Homogeneity:

There was minimal interstudy variance in the measurement of FEV1 for single-dose studies ($p = 0.62$) and for studies of longer duration ($p = 0.54$). No interstudy heterogeneity was seen for respiratory symptoms, for single-dose studies ($p = 1$) or for those with longer duration ($p = 0.99$).

Subgroup Analyses:

In order to evaluate the effect of treatment in patients with severe chronic airways obstruction, 6 trials that demonstrated an average baseline FEV1 of < 1.4 litres or < 50% normal predicted values were analysed separately (McGavin 1978; Sinclair 1979; Fogari 1990; Fenster 1983; Butland 1983; Wunderlich 1980). When the analysis was limited to those with severe obstruction there still was no significant difference in FEV1 treatment effect for single-dose trials (WMD -0.71% [95%CI, -5.69 to 4.27]) or for longer duration trials (WMD -3.11% [95%CI, -8.62 to 2.41]), and there was no increase in symptoms in any of these trials.

Another subgroup analysed patients who had COPD with a reversible component as demonstrated by an improvement in FEV1 of at least 15% after beta2-agonists (Adam 1982; Macquin-Mavier 1988; Dorow 1986b; von Wichert 1982; Dorow 1986a; Fogari 1990; Fenster 1983). When these 7 trials were analysed separately, there still was no significant change in FEV1 seen in single dose trials (WMD -1.8% [95%CI, -7.01 to 3.41]) or those of longer duration (WMD -1.26% [95%CI, -5.78 to 3.25]), and no increase in symptoms were found in any study.

In 8 of the trials, all participants had comorbid cardiovascular conditions such as hypertension or angina (Adam 1982; von Wichert 1982; Wunderlich 1980; Tivenius 1976; Ranchod 1982; Perks 1978; Anderson 1980; Macquin-Mavier 1988). When only these trials were included in the analysis, there was no significant FEV1 treatment effect seen for single dose studies (WMD -1.8% [95%CI, -7.01 to 3.41]) or for those of longer duration (WMD -4.20% [95%CI, -9.32 to 0.92]), and no respiratory symptoms were seen in the treatment group in any of the studies.

Sensitivity Analyses:

A sensitivity analysis was performed to evaluate the effect on FEV1 of including studies that did not provide placebo controls (Mc-

Gavin 1978; Sorbini 1982). When only placebo-controlled trials were included in the analysis for single-dose treatment (Adam 1982; Sinclair 1979) there was no significant change in any of the results, with less than 1% absolute difference in FEV1 treatment effect. All 4 of the longer-duration trials of FEV1 provided placebo controls, although 2 of these did not provide data on the baseline FEV1 prior to placebo administration (Dorow 1986a; Fogari 1990). When these trials were excluded, there was less than 2% absolute change in FEV1 treatment effect (WMD -4.29% [95%CI, -8.44 to -0.14]).

Another sensitivity analysis evaluated the effect of including trials that did not provide study SDs for the FEV1 treatment effect (McGavin 1978; Sinclair 1979; Fenster 1983; Fogari 1990; Ranchod 1982). Excluding trials that did not provide SD data did not significantly effect the results for single-dose trials (WMD -3.01% [95%CI, -7.12 to 1.09]), or for those of longer duration (WMD 2.06% [95%CI, -4.87 to 8.91]). Another analysis was performed by replacing the pooled SD with the lowest and highest available SD. For the single-dose trials and longer duration trials, the difference in results between the highest and lowest SD was not significantly different, with an absolute change in FEV1 of less than 1%.

DISCUSSION

Summary:

This meta-analysis pooled 20 homogeneous randomised, blinded controlled trials on the use of cardioselective beta-blockers in patients with COPD. These trials demonstrated that cardioselective beta-blockers, given as a single dose or for longer durations, produced no change in FEV1 or respiratory symptoms compared to placebo, and did not effect the FEV1 treatment response to beta2-agonists. These findings were unchanged in subgroup analyses of patients with severe COPD (FEV1 < 1.4 litres or < 50 % normal predicted values) or for those with a reversible obstructive component (FEV1 increase of > 15% to beta2-agonists). These findings are supported by a recent meta-analysis that demonstrated that cardioselective beta-blockers given to patients with reversible airway disease did not produce clinically significant adverse respiratory effects (Salpeter 2001).

Limitations of the Review:

This meta-analysis has several limitations, some that are similar to those found with most meta-analyses (Ionnidis 1999). The analysis only reports on published literature and is therefore subject to publication bias. Most of the studies were small and 80% of the participants were men. The randomisation process was not well delineated in many of the studies and some were single-blinded rather than double-blinded. A few studies did not have placebo controls, and many did not provide individual study standard deviations for FEV1 treatment effects. However, sensitivity analyses

were performed to evaluate the effect of including these trials and the results were found to be consistent throughout, due to the homogeneous nature of the individual trial results.

Generalisability and Applicability of Results:

This current meta-analysis indicates that the use of cardioselective beta-blockers is safe in patients who have COPD, with or without a reversible component. Treatment was also found to be safe for a subgroup of patients with concomitant angina, ischemic heart disease or hypertension. These findings are consistent with other studies that have investigated the use of beta-blockers in patients with cardiac disease and concomitant COPD or asthma and have found that these medicines were well tolerated (Mooss 1994; Quan 1983). Other trials evaluating the use of beta-blockers in hypertensive patients, many of whom had pulmonary disease, did not demonstrate a worsening of respiratory symptoms or FEV1 (Falliers 1985; George 1983; Formgren 1976; Krauss 1984). Chen and colleagues examined data from the Cooperative Cardiovascular Project on patients treated with a beta-blocker after a myocardial infarction and found no increase in hospitalizations for COPD or asthma exacerbations in patients one year after starting treatment (Chen 2001). Another study on survivors of myocardial infarction included 46,000 patients with asthma or COPD, and showed a significant reduction in total mortality for those treated with beta-blockers compared to those who were not (Gottlieb 1998).

The current standard of care is to avoid the use of beta-blockers in patients with reactive or obstructive airway disease (Tattersfield 1986; Tattersfield 1990; O'Malley 1991; Belli 1995; Craig 1996; JNC 1997). This reluctance to use beta-blockers is based on case reports of acute bronchospasm in patients with reversible airway disease precipitated by high doses of non-cardioselective beta-blockers (McNeill 1964; Zaid 1966; Anderson 1979; Raine 1981). Only a small fraction of patients with heart disease who would benefit from beta-blockers are currently given this treatment (Wang 1998; Soumerai 1997; Sial 1994; Krumholz 1998). A recent study by Heller and colleagues showed that COPD and asthma were the co-morbidities most commonly associated with beta-blockers being withheld in elderly patients after a myocardial infarction (Heller 2000).

Cardioselective beta-blockers such as atenolol, bisoprolol and metoprolol are at least 20 times more potent at blocking beta-1 receptors than beta-2 receptors (Wellstein 1987). The studies in this meta-analysis gave doses of beta-blockers ranging from therapeutic to supra-therapeutic doses, those that are not generally used for initiation of treatment. For example, subjects were given single doses of metoprolol or atenolol ranging from 50 to 200 mg, without a clinically apparent effect on respiratory function. However, it would be reasonable in clinical practice to start treatment with a low daily dose such as 25 mg of atenolol and titrate the dose up as needed.

The cardioselective beta-blockers used in this trial included those with and without intrinsic sympathomimetic activity. In the single-dose trials that measured FEV1 treatment effect, only beta1-blockers without intrinsic sympathomimetic activity were studied, so these could not be compared to those with sympathomimetic activity. In the longer duration trials, when cardioselective beta-blockers with intrinsic sympathomimetic activity (acebutolol and celiprolol) were compared to those without activity (atenolol and metoprolol), there was no significant change in FEV1 treatment effect (WMD 6.2% [95%CI, -0.7 to 13.1]). Of note, the cardiovascular benefits seen with beta-blockers appear to be lost when intrinsic sympathomimetic activity is present (Wadworth 1991).

Due to the proven mortality benefit of beta-blockers in numerous conditions, many of the other relative or absolute contraindications traditionally listed for beta-blockers have been questioned and disproved, including impaired left ventricular function, peripheral vascular disease, diabetes mellitus, depression, and advanced age (Lechat 1998; Gottlieb 1998; Radack 1991; Rosen-son 1993; Jonas 1996; Kjekshus 1990; Wicklmayr 1990; Bright 1992; Beto 1992; Krumholz 1999; Opie 1990). This meta-analysis suggests that cardioselective beta-blockers can safely be given to patients with COPD, even for those with a reversible component or with severe baseline obstruction. It is clear from this evidence that the proven benefit of cardioselective beta-blocker treatment far outweighs the risks in these patients, as found in the studies identified in this review.

AUTHORS' CONCLUSIONS

Implications for practice

Beta-blocker treatment reduces mortality in patients with cardiovascular disease. The available data from controlled trials suggest that cardioselective beta-blocker use in patients with COPD has no significant adverse effects on FEV1, respiratory symptoms or response to beta2-agonists, even for those with severe chronic airways obstruction.

Implications for research

From the accumulated evidence we have now, it is apparent that patients with COPD should not be excluded from future beta-blocker trials so that the treatment effect can be studied in this substantial population.

POTENTIAL CONFLICT OF INTEREST

None

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TABLES

Characteristics of included studies

Study	Adam 1982
Methods	Trial design: Double-blind, placebo-controlled cross-over.
Participants	Country: Australia. Setting: clinic. Treatment N: 20 Placebo N: 10 Age: 65.1. Sex: unclear. Inclusion: Hypertension with COPD on clinical grounds.
Interventions	Treatment: Single-dose metoprolol 100mg PO, atenolol 100mg. Comparison: placebo
Outcomes	Outcomes: FEV1 3.5 hours after drug, symptoms
Notes	Nonselectives studied: labetalol, propranolol
Allocation concealment	B – Unclear

Study	Anderson 1980
Methods	Trial design: Double-blind, placebo-controlled cross-over

Characteristics of included studies (Continued)

Participants	Country: Wales. Setting: clinic. Treatment N: 9 Placebo N: 9. Age: 59. Sex: unclear. Inclusion: Hypertension or angina with chronic bronchitis, PEFR < 70% predicted
Interventions	Treatment: Single-dose metoprolol 100mg PO, Comparison: placebo
Outcomes	Outcomes: peak flows measured from 15 to 180 minutes after drug, and symptoms
Notes	Nonselective studied: propranolol
Allocation concealment	D – Not used

Study **Beil 1977**

Methods	Trial design: Double-blind, placebo-controlled cross-over
Participants	Country: Germany. Setting: clinic. Treatment N: 44. Placebo N: 22. Age: 26-75. Sex: 82% males. Inclusion: chronic obstructive disease on clinical grounds, in remission phase
Interventions	Treatment: Single-dose atenolol 100mg, Comparison: placebo
Outcomes	Outcomes: Airway resistance, thoracic gas volume, pulse, blood pressure, and symptoms
Notes	Nonselective studied: propranolol
Allocation concealment	B – Unclear

Study **Butland 1983**

Methods	Trial design: Double-blind placebo-controlled cross-over
Participants	Country: United Kingdom. Setting: hospital. Treatment N: 24. Placebo N: 12. Age: 61. Sex: 83% male. Inclusion: Emphysema with severe airway obstruction, FEV1 <1L.
Interventions	Treatment: 4 weeks duration metoprolol 100mg/day PO, atenolo 100mg/day. Comparison: 4 weeks placebo. Single dose study not placebo controlled, excluded from symptom analysis
Outcomes	Outcomes: FEV1 measured with exercise, excluded from analysis. Symptoms
Notes	
Allocation concealment	B – Unclear

Study **Dorow 1986a**

Methods	Trial design: Single-blind + double-blind placebo-controlled cross-over
Participants	Country: Germany. Setting: University clinic. Treatment N: 34. Placebo N: 34. Age: unclear. Sex: unclear. Inclusion: Hypertension with reversible bronchial obstruction, FEV1 40-70% predicted, with >15% increase with beta-agonist
Interventions	Treatment: 12 weeks celiprolol 200-600 mg/day PO. Comparison: 4 weeks placebo
Outcomes	Outcomes: FEV1 measured at baseline, 4 weeks, 8 weeks. Note: Baseline FEV1 not recorded prior to placebo. Symptoms measured as change in number from baseline of incidents and days observed, so excluded from analysis
Notes	Other comparison studied: chlorthalidone
Allocation concealment	D – Not used

Study **Dorow 1986b**

Methods	Trial design: Double-blind, placebo-controlled cross-over
Participants	Country: Germany. Setting: University clinic. Treatment N: 24. Placebo N: 12. Age: 46. Sex: 92% male. Inclusion: COPD clinically stable with reversible component, FEV1 > 15% increase with beta-agonist, and angina

Characteristics of included studies (Continued)

Interventions	Treatment: Single-dose bisoprolol 20mg PO, atenolol 100mg. Comparison: placebo
Outcomes	Airway resistance, blood pressure, pulse. FEV1 reported in graph form, excluded from analysis. Symptoms.
Notes	
Allocation concealment	B – Unclear

Study Fenster 1983

Methods	Trial design: Single-blind placebo-controlled cross-over
Participants	Country: USA. Setting: Pulmonary clinic. Treatment N: 6. Placebo N: 6. Age: 48.6. Sex: 33% male. Inclusion: COPD with FEV1 < 60% predicted, reversible with > 15% increase with beta-agonist.
Interventions	Treatment: 1 week metoprolol, 200mg/day PO. Comparison: 1 week placebo
Outcomes	Outcomes: FEV1 at baseline, day 2, 5. Symptoms
Notes	No FEV1 standard deviations recorded.
Allocation concealment	D – Not used

Study Fogari 1990

Methods	Trial design: Single-blind, placebo-controlled cross-over
Participants	Country: Italy. Setting: University clinic. Treatment N: 20. Placebo N: 10. Age: 57. Sex: 100% male. Inclusion: Hypertension, and reversible COPD with FEV1 < 70%, >15% increase with beta-agonist
Interventions	Treatment: 1 week atenolol 100mg/day PO, celiprolol 200mg/day. Comparison: 2 weeks placebo
Outcomes	Outcomes: FEV1 measured at baseline and 1 week, symptoms. Note: Baseline FEV1 not recorded prior to placebo.
Notes	Nonselective studied: oxprenolol, propranolol. No FEV1 standard deviations recorded.
Allocation concealment	D – Not used

Study Lammers 1985a

Methods	Trial design: Single-blind + double-blind placebo-controlled cross-over
Participants	Country: Netherlands. Setting: outpatient clinic. Treatment N: 8. Placebo N: 8. Age: 52.7+/- 0.4. Sex: 88% male. Inclusion: Hypertension and COPD according to ATS guidelines.
Interventions	Treatment: 4 weeks metoprolol 100mg BID PO. Comparison: 4 weeks placebo
Outcomes	FEV1 measured in graph form at baseline, 2, 4 weeks, excluded from analysis. Symptoms
Notes	Nonselective studied: pindolol
Allocation concealment	D – Not used

Study Macquin-Mavier 1988

Methods	Trial design: Double-blind, placebo-controlled cross-over
Participants	Country: France. Setting: laboratory. Treatment N: 18. Placebo N: 9. Age: 38. Sex: 55% male. Inclusion: Smokers with chronic reversible airway obstruction, with FEV1 < 70% predicted, > 20% increase with beta-agonist.
Interventions	Treatment: Single-dose bisoprolol 10 mg PO, acebutolol 100mg. Comparison: placebo.
Outcomes	Specific airway conductance at baseline and each week. Symptoms
Notes	
Allocation concealment	B – Unclear

Characteristics of included studies (Continued)

Study	McGavin 1978
Methods	Trial design: Double-blind cross-over with baseline controls. No placebo
Participants	Country: United Kingdom. Setting: Hospital. Treatment N: 9. Placebo N: 0. Inclusion: Chronic airways obstruction with breathlessness, average FEV1 40% predicted. Response to propranolol excluded.
Interventions	Treatment: Single dose metoprolol 100mg PO. Comparison: propranolol (excluded)
Outcomes	Outcomes: FEV1 measured at baseline, 1, 6 hours after drug. Symptoms excluded, because no placebo.
Notes	Nonselective studied: propranolol. No FEV1 standard deviations recorded.
Allocation concealment	B – Unclear

Study	Perks 1978
Methods	Trial design: Double-blind, placebo-controlled cross-over
Participants	Country: United Kingdom. Setting: hospital. Treatment N: 20. Placebo N: 10. Age: 56.5, Sex: 80% male. Inclusion: Angina or hypertension with chronic airways obstruction on clinical grounds, some reversible.
Interventions	Treatment: Single-dose atenolol 50 + 100 mg PO, Comparison: placebo
Outcomes	FEV1 measurement in graph form at baseline, 15 minutes, then every hour for 3 hours, excluded from analysis. Symptoms
Notes	Nonselective studied: oxprenolol
Allocation concealment	B – Unclear

Study	Ranchod 1982
Methods	Trial design: Double-blind placebo-controlled cross-over
Participants	Country: South Africa. Setting: University clinic. Treatment N: 15. Placebo N: 15. Age: 39. Sex: unclear. Inclusion: Cigarette smokers with chronic bronchitis on clinical grounds with mild airflow obstruction, no reversibility.
Interventions	Treatment: 1 week atenolol 100mg/day PO. Comparison: placebo
Outcomes	FEV1 at baseline, 120 minutes, 7 days, symptoms
Notes	Nonselective studied: propranolol. No FEV1 standard deviations recorded.
Allocation concealment	B – Unclear

Study	Schanning 1976
Methods	Trial design: Double-blind, placebo-controlled, cross-over
Participants	Country: Norway. Setting: unclear. Treatment N: 20. Placebo N: 20. Age: 53.0. Sex: 85% male. Inclusion: Chronic obstructive lung disease on clinical grounds, stable phase.
Interventions	Treatment: Single-dose practolol 15 mg IV, Comparison: placebo IV
Outcomes	Outcomes: FEV1 measured at baseline and during 10 and 15 minutes of exercise, excluded from analysis. Symptoms
Notes	
Allocation concealment	B – Unclear

Study	Sinclair 1979
Methods	Trial design: Double-blind, placebo-controlled cross-over
Participants	Country: Scotland. Setting: laboratory. Treatment N: 10. Placebo N: 10. Age: 63. Sex: unclear. Inclusion: Chronic bronchitis, FEV1 < 70% predicted

Characteristics of included studies (Continued)

Interventions	Treatment: Single-dose Metoprolol 0.12mg/kg IV. Comparison: placebo IV.
Outcomes	Outcomes: FEV1 measured at baseline, every 15 minutes for 1 hour, symptoms
Notes	Nonselective studied: propranolol. No FEV1 standard deviations recorded.
Allocation concealment	B – Unclear

Study Sorbini 1982

Methods	Trial design: Double-blind cross-over with baseline controls. No placebo
Participants	Country: Italy. Setting: unclear. Treatment N: 32. Placebo N: 0. Inclusion: Chronic obstructive lung disease or asthma on clinical grounds, with long history of attacks, now in remission phase.
Interventions	Treatment: Single-dose metoprolol 50mg PO, 100mg, 150mg, 200 mg. Comparison: none
Outcomes	Outcomes: FEV1, forced vital capacity, pulse, airway resistance, peak flow at baseline, every hour for 3 hours, 6 hours. Symptoms excluded because no placebo
Notes	
Allocation concealment	B – Unclear

Study Tivenius 1976

Methods	Trial design: Double-blind placebo-controlled cross-over
Participants	Country: Sweden. Setting: lung clinic. Treatment N: 12. Placebo N: 12. Age: 53. Sex: 92% male. Inclusion: COPD on clinical grounds, recovering from acute exacerbation.
Interventions	Treatment: 2 days metoprolol 50 mg TID PO, Comparison: placebo
Outcomes	Outcomes: FEV1, forced vital capacity, pulse, blood pressure measured at 2 hours and 2 days, reported without baseline, excluded from analysis. Symptoms
Notes	Nonselective studied: propranolol
Allocation concealment	B – Unclear

Study Wunderlich 1980

Methods	Trial design: Double-blind placebo-controlled cross-over
Participants	Country: Germany. Setting: clinic. Treatment N: 35. Placebo N: 35. Age: 61.9. Sex: 69% male. Inclusion: Hypertension or ischemic heart disease and COPD, on clinical grounds.
Interventions	Treatment: 2 days metoprolol 100mg BID PO. Comparison: 2 days placebo
Outcomes	Outcomes: FEV1, forced residual capacity, airway resistance, pulse, blood pressure measured at baseline and every day for 2 days, measured in graph form so excluded from analysis. Symptoms
Notes	Nonselective studied: propranolol
Allocation concealment	B – Unclear

Study van der Woude 2005

Methods	Trial design: Double-blind, placebo-controlled cross-over
Participants	Country: Netherlands Setting: Single center Treatment N: 15 Placebo N: 15
Interventions	Treatment: 4 days metoprolol 100 mg PO BID and celiprolol 200 mg PO BID. Comparison: 4 days Placebo

Outcomes	Outcomes: FEV1 baseline, after treatment and 30 minutes after formoterol, and PC20
Notes	Nonselective studied: propranolol
Allocation concealment	B – Unclear

Study	von Wichert 1982
Methods	Trial design: Double-blind, placebo-controlled cross-over
Participants	Country: Germany. Setting: University clinic. Treatment N: 12. Placebo N: 12. Age: 45-55. Sex: 83% male. Inclusion: Reversible chronic airways obstruction with chronic bronchitis according to WHO, >15% with beta-agonist, positive acetylcholine test.
Interventions	Treatment: Single-dose metoprolol 100mg PO. Comparison: placebo
Outcomes	Outcomes: Total airway resistance measured at baseline, 90 minutes, after beta-agonist. Symptoms
Notes	Nonselective studied: pinpolol
Allocation concealment	B – Unclear

Characteristics of excluded studies

Study	Reason for exclusion
Abraham 1981	Not randomized
Addis 1976	No cardioselective blocker
Anavekar 1982	No cardioselective blocker
Chester 1981	No cardioselective blocker
Clague 1984	No FEV1 data or placebo-controls
Dal Negro 1981	Not blinded
Dal Negro 1986	Not blinded
Dorow 1984	Not blinded
Dorow 1986c	Not blinded
George 1983	No cardioselective blocker
Johnsson 1976	Review
Lois 1997	Review
Lois 1999	Review
Meier 1966a	No cardioselective blocker
Meier 1966b	Duplicate of 1986a
Nordstrom 1975	No cardioselective blocker
Quan 1983	Not randomized
Ulmer 1976	No cardioselective blocker
Wettengel 1970	No cardioselective blocker
van Herwaarden 1983	Review

ADDITIONAL TABLES

Table 01. Beta-blocker Categories

Nonselective (- ISA)	Nonselective (+ISA)	Selective (-ISA)	Selective (+ ISA)
Propranolol	Oxprenolol	Atenolol	Celiprolol (+ alpha block)
Timolol	Pindolol	Metoprolol	Acebutolol
Nadolol	Dilevalol	Bisoprolol	Xamoterol
Sotolol (antiarrhythmic)	Prenalterol	Practolol	
Ibutomide (+ alpha block)	Labetolol (+ alpha block)	Esmolol	
		Pafenolol	
		Tolamolol	
		Bevantolol (+ alpha agonist)	

ANALYSES

Comparison 01. Beta-blocker vs Placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Single-dose FEV1 treatment effect (Treatment minus Placebo, % change from baseline)	4	108	Weighted Mean Difference (Fixed) 95% CI	-2.08 [-5.25, 1.09]
02 Single-dose respiratory symptoms (Participants with symptoms, Treatment minus Placebo)	9	301	Risk Difference (Fixed) 95% CI	0.00 [-0.04, 0.04]
03 Longer duration FEV1 treatment effect (Treatment minus Placebo, % change from baseline)	5	170	Weighted Mean Difference (Fixed) 95% CI	-2.39 [-5.69, 0.91]
04 Longer duration respiratory symptoms (Participants with symptoms, Treatment minus Placebo)	8	224	Risk Difference (Fixed) 95% CI	0.00 [-0.05, 0.05]
05 SUBGROUP: Severe COPD, Single-dose FEV1 treatment effect (Treatment minus Placebo, % change)	2	38	Weighted Mean Difference (Fixed) 95% CI	-0.71 [-5.69, 4.27]
06 SUBGROUP: Severe COPD, Longer duration FEV1 treatment effect (Treatment minus Placebo, % change)	2	42	Weighted Mean Difference (Fixed) 95% CI	-3.11 [-8.62, 2.41]
07 SUBGROUP: Reversible airway disease, Single-dose FEV1 treatment effect (Treatment minus Placebo, % change)	1	30	Weighted Mean Difference (Fixed) 95% CI	-1.80 [-7.01, 3.41]

08 SUBGROUP: Reversible airway disease, Longer duration FEV1 treatment effect (Treatment minus Placebo, % change)	3	110	Weighted Mean Difference (Fixed) 95% CI	-1.26 [-5.78, 3.25]
09 SUBGROUP: Cardiovascular conditions, Single-dose FEV1 treatment effect (Treatment minus Placebo, % change)	1	30	Weighted Mean Difference (Fixed) 95% CI	-1.80 [-7.01, 3.41]
10 SUBGROUP: Cardiovascular disease, Longer duration FEV1 treatment effect (Treatment minus Placebo, % change)	1	30	Weighted Mean Difference (Fixed) 95% CI	-4.20 [-9.32, 0.92]

Comparison 02. Beta-blocker + agonist vs Placebo + agonist

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Single-dose Beta-agonist treatment effect (Treatment-agonist effect minus Placebo-agonist effect, % change)	2	50	Weighted Mean Difference (Fixed) 95% CI	-1.21 [-10.97, 8.56]
02 Longer duration Beta-agonist treatment effect (Treatment-agonist effect minus Placebo-agonist effect,% change)	2	60	Weighted Mean Difference (Fixed) 95% CI	1.12 [-4.97, 7.20]

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic beta-Antagonists [*therapeutic use]; Forced Expiratory Volume; Pulmonary Disease, Chronic Obstructive [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans

COVER SHEET

Title	Cardioselective beta-blockers for chronic obstructive pulmonary disease
Authors	Salpeter S, Ormiston T, Salpeter E
Contribution of author(s)	Shelley Salpeter: Developed review protocol Search strategy Trial selection Data extraction Manuscript preparation Management of Revman protocol Thomas Ormiston: Search strategy Trial selection Data extraction

	Manuscript preparation Edwin Salpeter: Data analysis Statistical management Manuscript preparation
Issue protocol first published	2000/2
Review first published	2001/2
Date of most recent amendment	04 July 2005
Date of most recent SUBSTANTIVE amendment	04 July 2005
What's New	One new study met the inclusion criteria (van der Woude 2005). The results and conclusions of the review are not changed by the additional data.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	01 May 2005
Date authors' conclusions section amended	Information not supplied by author
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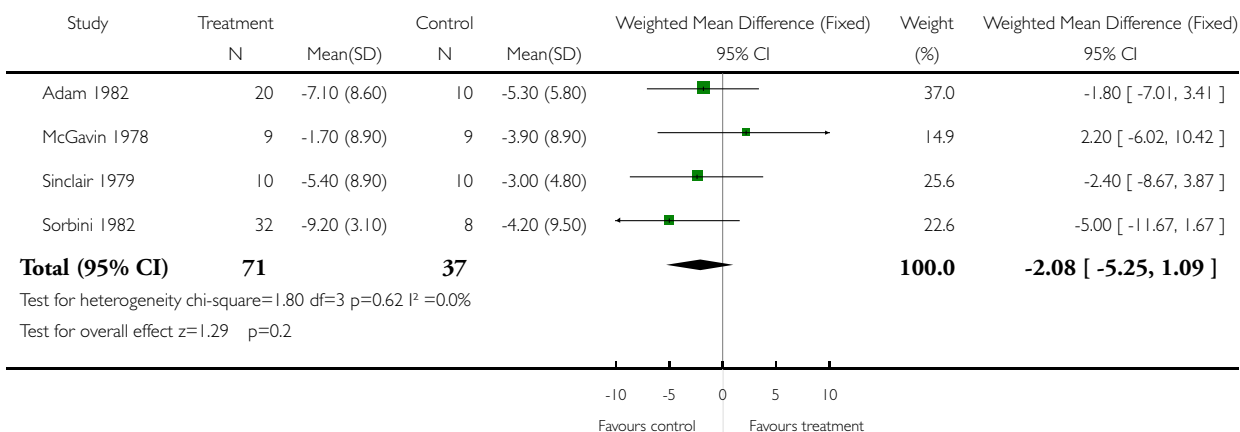
GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Beta-blocker vs Placebo, Outcome 01 Single-dose FEV1 treatment effect (Treatment minus Placebo, % change from baseline)

Review: Cardioselective beta-blockers for chronic obstructive pulmonary disease

Comparison: 01 Beta-blocker vs Placebo

Outcome: 01 Single-dose FEV1 treatment effect (Treatment minus Placebo, % change from baseline)

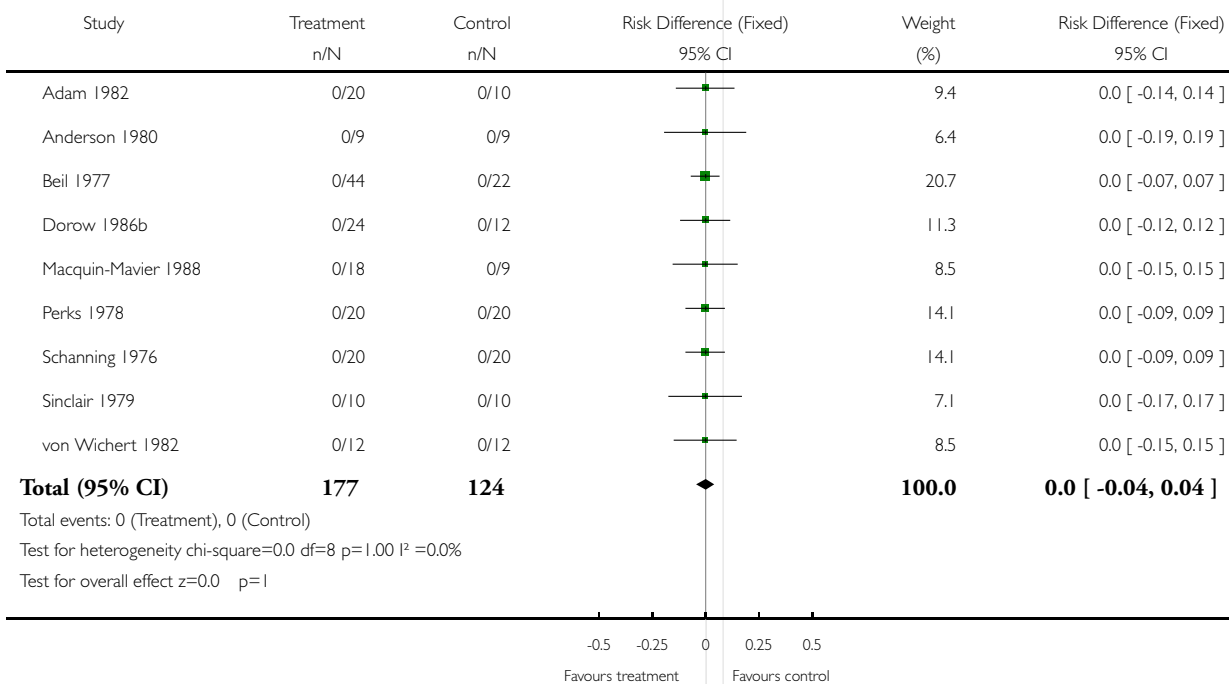


Analysis 01.02. Comparison 01 Beta-blocker vs Placebo, Outcome 02 Single-dose respiratory symptoms (Participants with symptoms, Treatment minus Placebo)

Review: Cardioselective beta-blockers for chronic obstructive pulmonary disease

Comparison: 01 Beta-blocker vs Placebo

Outcome: 02 Single-dose respiratory symptoms (Participants with symptoms, Treatment minus Placebo)

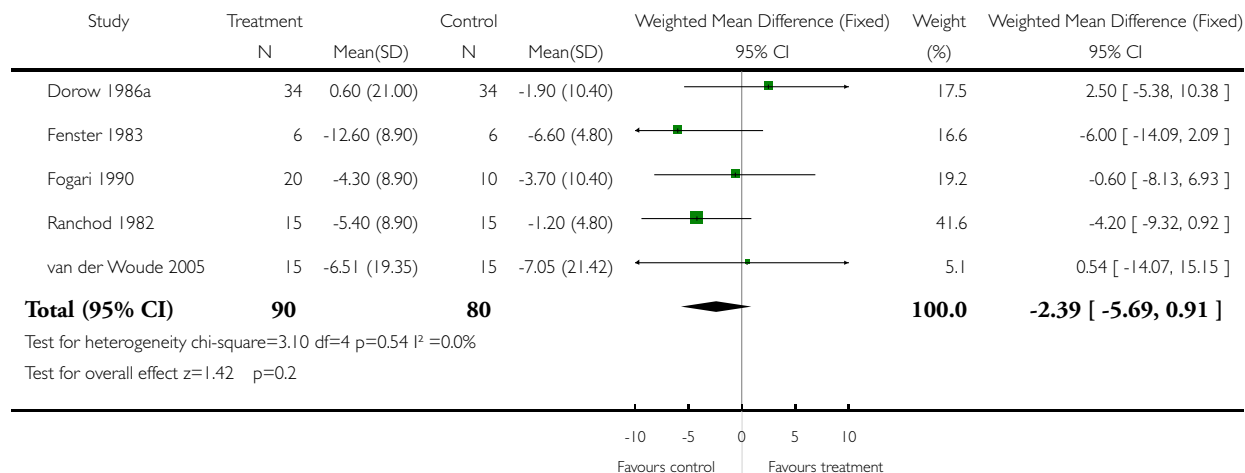


Analysis 01.03. Comparison 01 Beta-blocker vs Placebo, Outcome 03 Longer duration FEV1 treatment effect (Treatment minus Placebo, % change from baseline)

Review: Cardioselective beta-blockers for chronic obstructive pulmonary disease

Comparison: 01 Beta-blocker vs Placebo

Outcome: 03 Longer duration FEV1 treatment effect (Treatment minus Placebo, % change from baseline)

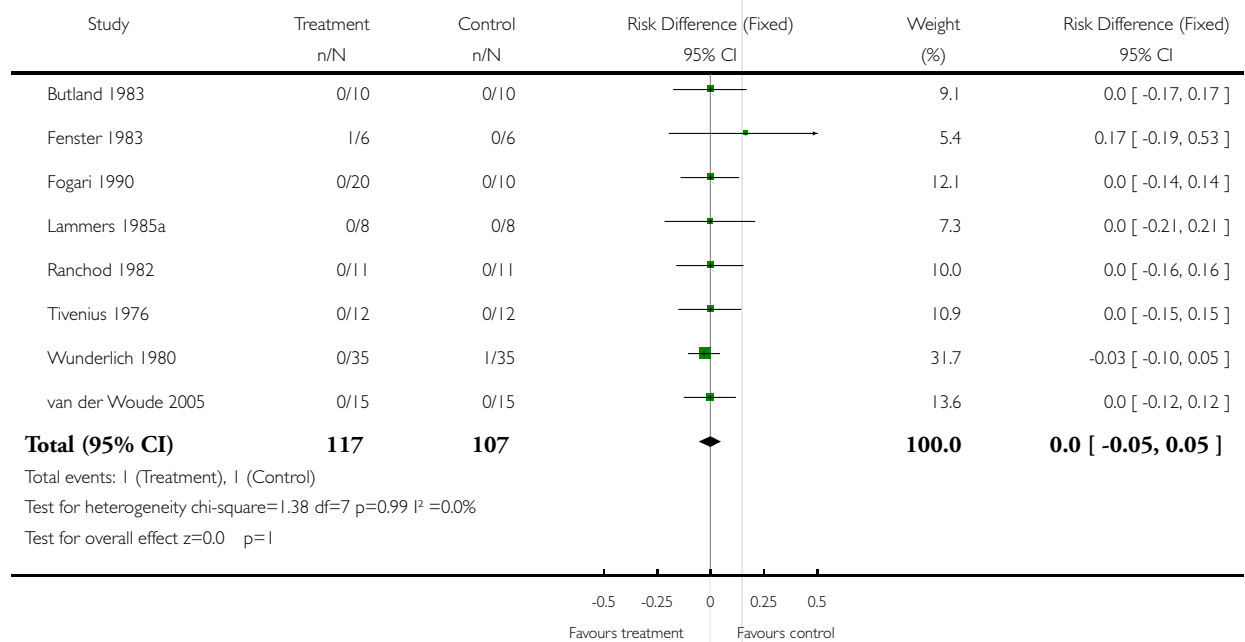


Analysis 01.04. Comparison 01 Beta-blocker vs Placebo, Outcome 04 Longer duration respiratory symptoms (Participants with symptoms, Treatment minus Placebo)

Review: Cardioselective beta-blockers for chronic obstructive pulmonary disease

Comparison: 01 Beta-blocker vs Placebo

Outcome: 04 Longer duration respiratory symptoms (Participants with symptoms, Treatment minus Placebo)

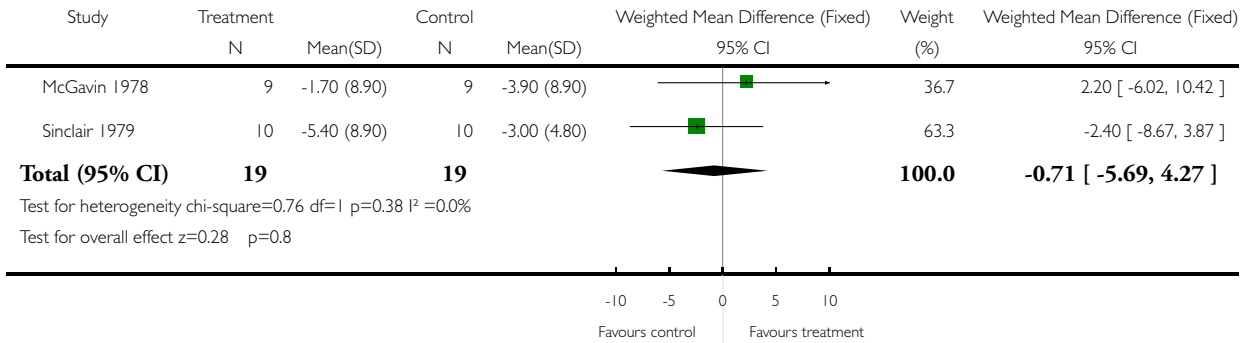


Analysis 01.05. Comparison 01 Beta-blocker vs Placebo, Outcome 05 SUBGROUP: Severe COPD, Single-dose FEV1 treatment effect (Treatment minus Placebo, % change)

Review: Cardioselective beta-blockers for chronic obstructive pulmonary disease

Comparison: 01 Beta-blocker vs Placebo

Outcome: 05 SUBGROUP: Severe COPD, Single-dose FEV1 treatment effect (Treatment minus Placebo, % change)

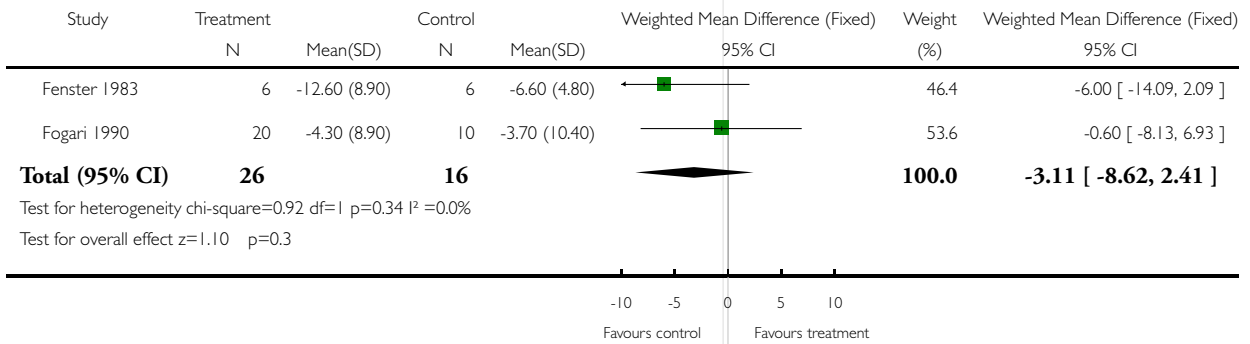


Analysis 01.06. Comparison 01 Beta-blocker vs Placebo, Outcome 06 SUBGROUP: Severe COPD, Longer duration FEV1 treatment effect (Treatment minus Placebo, % change)

Review: Cardioselective beta-blockers for chronic obstructive pulmonary disease

Comparison: 01 Beta-blocker vs Placebo

Outcome: 06 SUBGROUP: Severe COPD, Longer duration FEV1 treatment effect (Treatment minus Placebo, % change)

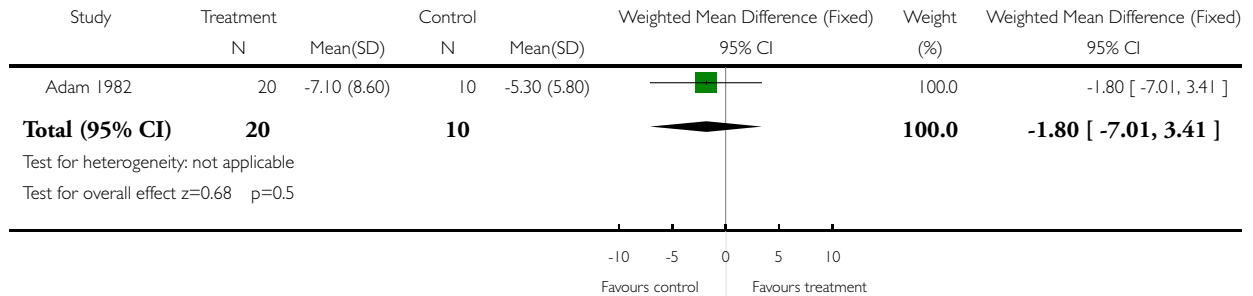


Analysis 01.07. Comparison 01 Beta-blocker vs Placebo, Outcome 07 SUBGROUP: Reversible airway disease, Single-dose FEV1 treatment effect (Treatment minus Placebo, % change)

Review: Cardioselective beta-blockers for chronic obstructive pulmonary disease

Comparison: 01 Beta-blocker vs Placebo

Outcome: 07 SUBGROUP: Reversible airway disease, Single-dose FEV1 treatment effect (Treatment minus Placebo, % change)

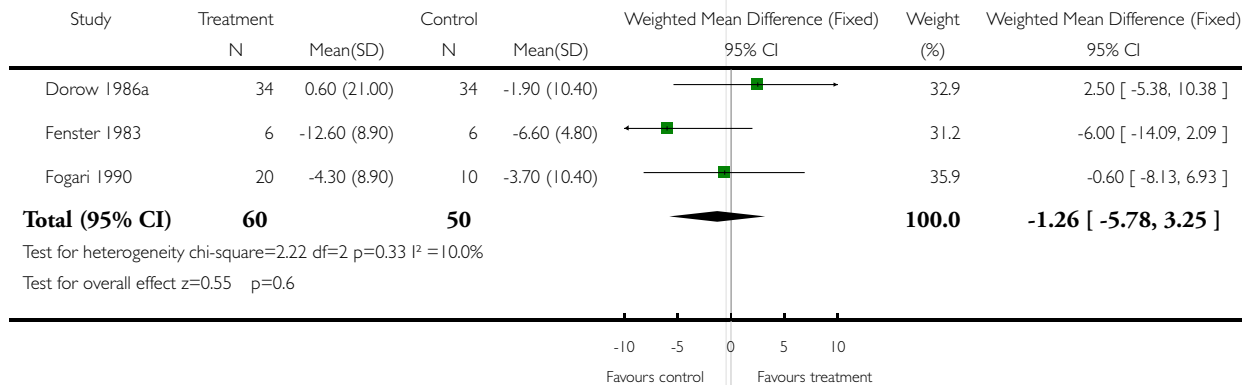


Analysis 01.08. Comparison 01 Beta-blocker vs Placebo, Outcome 08 SUBGROUP: Reversible airway disease, Longer duration FEV1 treatment effect (Treatment minus Placebo, % change)

Review: Cardioselective beta-blockers for chronic obstructive pulmonary disease

Comparison: 01 Beta-blocker vs Placebo

Outcome: 08 SUBGROUP: Reversible airway disease, Longer duration FEV1 treatment effect (Treatment minus Placebo, % change)

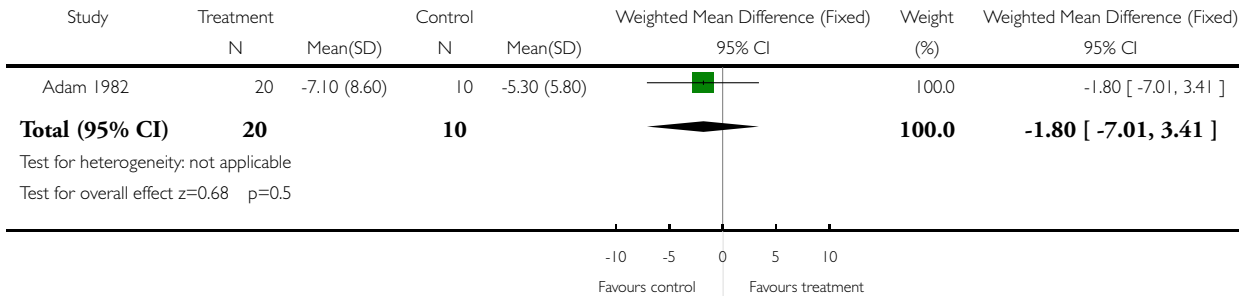


Analysis 01.09. Comparison 01 Beta-blocker vs Placebo, Outcome 09 SUBGROUP: Cardiovascular conditions, Single-dose FEV1 treatment effect (Treatment minus Placebo, % change)

Review: Cardioselective beta-blockers for chronic obstructive pulmonary disease

Comparison: 01 Beta-blocker vs Placebo

Outcome: 09 SUBGROUP: Cardiovascular conditions, Single-dose FEV1 treatment effect (Treatment minus Placebo, % change)

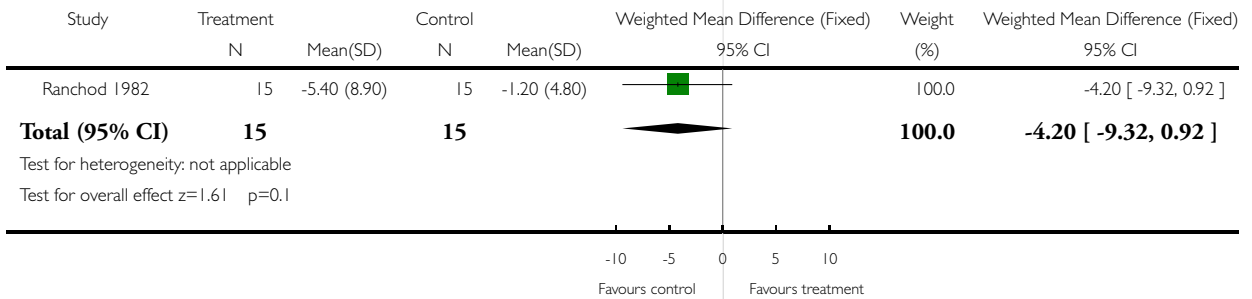


Analysis 01.10. Comparison 01 Beta-blocker vs Placebo, Outcome 10 SUBGROUP: Cardiovascular disease, Longer duration FEV1 treatment effect (Treatment minus Placebo, % change)

Review: Cardioselective beta-blockers for chronic obstructive pulmonary disease

Comparison: 01 Beta-blocker vs Placebo

Outcome: 10 SUBGROUP: Cardiovascular disease, Longer duration FEV1 treatment effect (Treatment minus Placebo, % change)

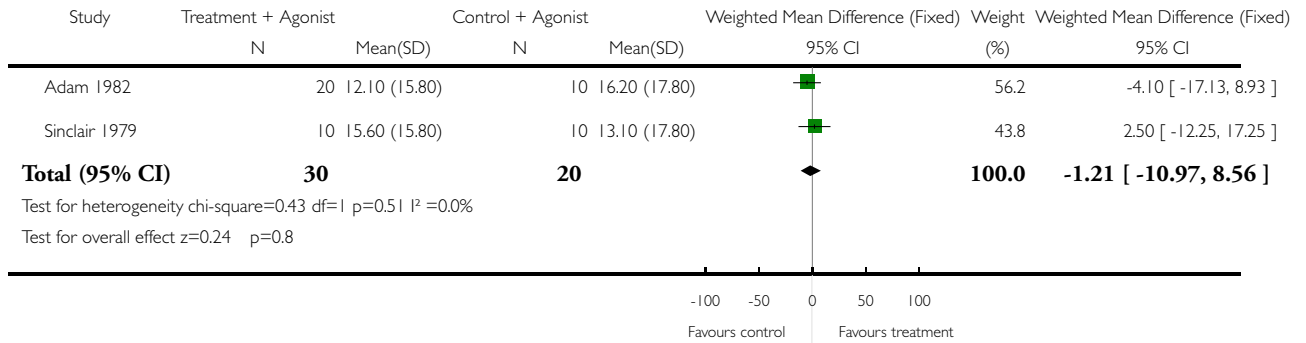


Analysis 02.01. Comparison 02 Beta-blocker + agonist vs Placebo + agonist, Outcome 01 Single-dose Beta-agonist treatment effect (Treatment-agonist effect minus Placebo-agonist effect, % change)

Review: Cardioselective beta-blockers for chronic obstructive pulmonary disease

Comparison: 02 Beta-blocker + agonist vs Placebo + agonist

Outcome: 01 Single-dose Beta-agonist treatment effect (Treatment-agonist effect minus Placebo-agonist effect, % change)



Analysis 02.02. Comparison 02 Beta-blocker + agonist vs Placebo + agonist, Outcome 02 Longer duration Beta-agonist treatment effect (Treatment-agonist effect minus Placebo-agonist effect,% change)

Review: Cardioselective beta-blockers for chronic obstructive pulmonary disease

Comparison: 02 Beta-blocker + agonist vs Placebo + agonist

Outcome: 02 Longer duration Beta-agonist treatment effect (Treatment-agonist effect minus Placebo-agonist effect,% change)

