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Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension.

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[Intervention Review]

Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

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ABSTRACT

Background

Partial agonists are a subclass of beta blockers used to treat hypertension in many countries. Partial agonist act by stimulating beta receptors when they are quiescent and blocking beta receptors when they are active. The blood pressure (BP) lowering effect of partial agonist beta blockers has not been quantified.

Objectives

To quantify the dose-related effects of various partial agonists beta blockers on systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate versus placebo in patients with primary hypertension.

Search methods

We searched the Hypertension Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, MEDLINE In-Process, EMBASE and ClinicalTrials.gov for randomized controlled trials up to October 2014. The WHO International Clinical Trials Registry Platform (ICTRP) is searched for inclusion in the Group's Specialised Register.

Selection criteria

Randomized double-blinded placebo-controlled parallel or cross-over trials. Studies must contain a partial agonist monotherapy arm with fixed dose. Patients enrolled into the studies must have primary hypertension at baseline (defined as SBP/DBP $\geq$ 140/90 mmHg). Duration of studies must be between three to 12 weeks.

Data collection and analysis

Two authors (GW and HB) confirmed the inclusion of studies and extracted the data independently.

Main results

Thirteen randomized double-blinded placebo-controlled trials that examined the blood pressure lowering efficacy of six partial agonists in 605 hypertensive patients were included in this review. Five of the included studies were parallel studies and the other eight were cross-over studies. The overall risk of bias is high in this review due to the small sample size and high risk of detection bias. Pindolol, celiprolol and alprenolol lowered SBP and DBP compared to placebo. Acebutolol lowered SBP but there was no clear evidence that it lowered DBP. There was no clear evidence that pindolol and oxprenolol lowered SBP or DBP. Other than for celiprolol, sample sizes

were generally small increasing the uncertainty in findings for individual agents versus placebo. In patients with moderate to severe hypertension, partial agonists (considered as a subclass) lowered peak BP by an average of 8 mmHg systolic (95% CI, -10 to -6, *very low quality evidence*), 4 mmHg diastolic (95%CI, -5 to -3, *very low quality evidence*) and reduced heart rate by five beats per minute (95%CI, -6 to -4, *very low quality evidence*). Higher dose partial agonists did not appear to provide additional BP lowering effects compared to lower dose. The maximum BP lowering effect of the overall subclass occurred at the starting dose. Partial agonists reduced pulse pressure by 4 mmHg (95% CI, -5 to -2, *very low evidence*). Only one study reported withdrawal due to adverse effects, the risk ratio (95% confidence interval) was 0.72 (0.07, 7.67).

Authors' conclusions

There was very low quality evidence that in patients with moderate to severe hypertension, partial agonists lowered peak BP by an average of 8/4 mmHg and reduced heart rate by five beats per minute. There was no evidence of a greater effect at doses higher than the initial doses. This estimate was probably exaggerated as it was subject to a high risk of bias. Based on the indirect comparison of the results in this review and two Cochrane reviews on angiotensin-converting-enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), which also used similar inclusion criteria as this review, the BP lowering effect appeared to be less than the effect in patients with mild to moderate elevated BP who were taking ACE inhibitors and ARBs based on an indirect comparison. Withdrawals due to adverse effects were only reported in one trial so it is impossible to assess the harm of these drugs.

PLAIN LANGUAGE SUMMARY

Partial agonists for the treatment of high blood pressure.

Background

Partial agonists are a subclass of beta blockers used for treatment of high blood pressure. Drugs that belong to this class included acebutolol (Sectral), pindolol (Visken) and celiprolol (Cardem). We examined how much this class of drugs lowers blood pressure.

Study characteristics

We developed a comprehensive search strategy to search relevant scientific databases for clinical trials and found 13 trials that randomly assigned 605 high blood pressure patients to either fixed-dose partial agonist treatment or placebo for up to 12 weeks.

Key results

On average, partial agonists lowered blood pressure by eight points in systolic and four points in diastolic pressure in patient with moderate to severe high blood pressure. We did not find any evidence showing that doses higher than the recommended starting doses would further lower blood pressure. On average, partial agonists lowered pulse pressure by 4 mmHg. The included studies generally did not report side effects serious enough that lead to termination of treatment. It was not clear whether partial agonists provide more side effects serious enough that lead to withdrawal compared to placebo.

Quality of the evidence

The quality of evidence is very low due to small sample size and high risk of bias.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Blood pressure lowering effects of partial agonists compared with placebo for primary hypertension			
Patient or population: Adults with primary hypertension Intervention: Partial agonists Comparison: Placebo			
Outcomes	Mean estimates of 1x and 2x starting dose (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
Decrease in systolic blood pressure	-8.1 [-10.1 to -6.1] ^{1,2,3,4}	490 (10)	Very low ^{5,6,7}
Decrease in diastolic blood pressure	-4.0 [-5.1 to -2.9] ^{1,2,3,4}	490 (10)	Very low ^{5,6,7}
Decrease in heart rate	-4.9 [-6.2 to -3.7] ^{2,3}	256 (7)	Very low ^{5,6,7}
Decrease in pulse pressure	-3.6 [-5.3 to -1.9] ^{1,2}	490 (10)	Very low ^{5,6,7,8}
Withdrawal due to adverse effect	RR [95%CI]: 0.72 [0.07 to 7.67] ⁹	117 (1)	Very low ^{5,6,10}
95% CI: 95% confidence interval; RR: relative risk			
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.			
Footnotes			
1. Test for subgroup differences showed that 1x and 2x starting dose subgroups were not significantly different from each other. 2. The recommended starting and 2x starting contained most of the data for this class. Combining them provided the best estimate of the overall subclass effect. 3. BP was measured at peak hours. 4. Weighted mean baseline BP of included studies was 175/107 mmHg. 5. Quality of evidence was downgraded by one level due to small sample size and wide confidence intervals. 6. Quality of evidence was downgraded by one level due to high or unknown risk of detection bias caused by loss of blinding.			

7. Quality of evidence was downgraded by one level due to high risk of publication bias.
8. None of the studies included reported pulse pressure. Pulse pressure was calculated by subtracting DBP from SBP.
9. Withdrawal due to adverse effect was estimated based on one trial from bopindolol.
10. Quality of evidence was downgraded by one level due to high risk of reporting bias.

BACKGROUND

Description of the condition

Elevated blood pressure is a highly prevalent condition that is associated with an increased risk of adverse cardiovascular events including stroke, myocardial infarction, congestive heart failure and renal failure. Antihypertensive drug treatment has been shown to reduce the incidence of these adverse events. There are a number of classes of antihypertensive drugs used to treat elevated blood pressure. Beta adrenergic receptor blockers (beta blockers) are one of these classes of drugs.

Description of the intervention

Beta-blockers were originally marketed and used to treat angina. During their use in angina patients, it was discovered that they also lower blood pressure. Since then, they have received clinical attention because of their proven effectiveness for certain arrhythmias and to prevent recurrence in patients who have had a myocardial infarction.

Five previous published systematic reviews are relevant to this proposed review. [Wright 2000](#) assessed the mortality and morbidity associated with different types of beta blockers. He found that patients treated with non-selective beta blockers post myocardial infarction had a statistically significant reduction in total mortality as compared to placebo, whereas those treated with beta₁-selective beta blockers or partial agonist beta-blockers did not. A recent review assessed the effects of beta adrenergic blocking agents on morbidity and mortality in adults with hypertension ([Wiysonge 2007](#)). This review concluded that beta blockers are not the best class of drugs to use as first-line antihypertensive therapy. However, it is possible that these findings were related to beta₁-selective beta blockers, as atenolol was the beta-blocker used in 75% of the trials.

Two systematic reviews have assessed the effects of beta-blockers on blood pressure. A Cochrane systematic review on beta blockers in hypertension during pregnancy ([Magee 2003](#)) showed that oral beta-blockers decrease the incidence of severe hypertension and the need for additional antihypertensive therapy. A systematic review of the dose-response blood pressure lowering effect of beta blocker drugs and other antihypertensive drugs ([Law 2005](#)) did not differentiate between the different classes of beta-blockers. Finally, a systematic review of the blood pressure lowering efficacy of beta-blockers as a second-line drug also did not differentiate between the different classes of beta-blockers ([Chen 2010](#)).

How the intervention might work

Beta adrenergic receptors are present in many body systems including the heart, blood vessels, kidneys, and nervous system. At the

present time, the mechanism whereby beta-blockers lower blood pressure is not known, though many hypothetical mechanisms have been proposed. Beta blockers could lower blood pressure by decreasing cardiac output, reducing renin production, modulating the sympathetic nervous system or other mechanisms. It is likely to be a combination of mechanisms that lead to the blood pressure lowering effect.

Beta-blockers were designed to competitively inhibit adrenergic beta receptors, thus modulating sympathetic nervous system activity. There are three main classes of beta receptors; beta-1, beta-2 and beta-3. Currently, there are no known selective antagonists for beta-3 receptors. Some beta blockers have partial agonist activity. The main effect of partial agonists is inhibition during beta-receptors stimulation, and activation when the beta receptors are quiescent. Drugs in this class can be non-selective or beta-₁ selective but do not cause any alpha blocking effects.

Why it is important to do this review

Since it is probable that beta blockers with different mechanisms of action have different effects to reduce morbidity and mortality, it is crucial to determine whether they have different abilities to lower blood pressure. No published review has compared the blood pressure lowering effect of beta blockers based on their mechanism of action. If beta blockers with different beta receptor selectivity lower blood pressure differently, it would provide useful information towards understanding the mechanism by which they lower blood pressure.

Furthermore, since blood pressure measurements are used on a daily basis by physicians managing patients with high blood pressure, it is important to accurately assess the magnitude of blood pressure lowering effects of beta blockers, both individually and as a subclass. The results from this review will be compared to the reviews of the non-selective beta blockers and the beta-₁ selective beta blockers. The information found in this review will be useful for clinicians, researchers designing future drug trials and authors of other systematic reviews.

OBJECTIVES

Primary objective

To quantify the dose-related effects and types of partial agonist beta adrenergic receptor blockers (partial agonists) on systolic and diastolic blood pressure versus placebo in patients with primary hypertension.

Secondary objectives

To determine dose-related effects of partial agonist on variability of blood pressure; pulse pressure, heart rate and withdrawals due to adverse effects (WDAEs).

1. To determine dose-related effects of partial agonist beta adrenergic receptor blockers on variability of blood pressure.
2. To determine dose-related effects of partial agonist beta adrenergic receptor blockers on pulse pressure.
3. To quantify dose-related effects of partial agonist beta adrenergic receptor blockers on heart rate.
4. To quantify the effects of partial agonist beta adrenergic receptor blockers at different doses on WDAEs.

METHODS

Criteria for considering studies for this review

Types of studies

Study design must meet the following criteria:

- placebo-controlled;
- random allocation to beta adrenergic receptor blocker group and placebo group;
- parallel or cross-over design;
- double blinded;
- duration of follow-up of at least three weeks;
- blood pressure measurements at baseline (following washout) and at one or more time points between three to 12 weeks after starting treatment.

Types of participants

Participants must have a baseline blood pressure of at least 140 mmHg systolic and/or a diastolic blood pressure of at least 90 mmHg, measured in a standard way. Patients must not have creatinine levels greater than 1.5 times the normal level. Participants must not be restricted by age, gender, baseline risk or any other co-morbid conditions.

Types of interventions

Fixed-dose monotherapy with any beta adrenergic receptor blocker that has partial agonist activity, including acebutolol, celiprolol, oxprenolol, pindolol, alprenolol and bopindolol.

Data from trials in which titration to a higher dose was based on blood pressure response were not eligible.

Types of outcome measures

Primary outcomes

Change in trough (13 to 26 hours after the dose) and/or peak (one to 12 hours after the dose) systolic and diastolic blood pressure compared to placebo. If blood pressure measurements were available at more than one time point, the weighted means of blood pressures taken in the three to 12-week range were used.

Secondary outcomes

1. Change in standard deviation compared to placebo.
2. Change in pulse pressure compared to placebo.
3. Change in heart rate compared to placebo.
4. Number of patients who withdraw due to adverse events (WDAE) compared to placebo.

Search methods for identification of studies

The Database of Abstracts of Reviews of Effects (DARE) was searched for related reviews. Previously published meta-analyses on dose-response of beta adrenergic receptor blockers were used to help identify references to trials.

The Hypertension Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 9), MEDLINE (1946 - October 2014), EMBASE (1974 - October 2014) and ClinicalTrials.gov (all years to October 2014) were searched for randomized controlled trials. No language restrictions were applied. The WHO International Clinical Trials Registry Platform (ICTRP) is searched for inclusion in the Group's Specialised Register.

A modified, expanded version of the standard search strategy of the Hypertension Group with additional terms related to beta adrenergic receptor blockers in general and all the specific drugs listed above was used to identify the relevant articles. The MEDLINE strategy ([Appendix 1](#)) was translated into CENTRAL ([Appendix 2](#)), EMBASE ([Appendix 3](#)), ClinicalTrials.gov ([Appendix 4](#)), and the Hypertension Group Specialised Register ([Appendix 5](#)).

The initial search of all the databases was performed to identify citations with potential relevance. The initial screen of these abstracts excluded articles whose titles and/or abstracts were clearly irrelevant. The full text of remaining articles were retrieved (and translated into English where required). The bibliographies of pertinent articles, reviews and texts were searched for additional citations. Two review authors independently assessed the eligibility of the trials using a trial selection form. A third review author resolved discrepancies.

Data collection and analysis

Selection of studies

References and abstracts of search results were imported to Reference Manager 11 software. Selection of studies was based on the criteria listed above.

Data extraction and management

Two review authors independently extracted data using a standard form, and then cross-checked the results. All numeric calculations and graphic interpolations were confirmed by a second person.

Assessment of risk of bias in included studies

Standard quality measures were not useful to distinguish between trials meeting the strict entry criteria of this review (Jadad 1996). We assessed the risk of bias for each trial using 'Risk of bias' tables.

Measures of treatment effect

The position of the patient during blood pressure measurement may affect the blood pressure lowering effect. However, in order not to lose valuable data if only one position was reported, data from that position were collected. When blood pressure measurement data were available from more than one position, sitting blood pressure was the first preference. If both standing and supine data were available, standing blood pressure data were used.

Dealing with missing data

Attempts were made to contact study authors for missing information in the included studies (using email, letter and/or fax). In the case of missing standard deviation of the change in blood pressure, the standard deviation was imputed based on the information in the same trial or from other trials using the same drug. We used the following hierarchy (listed from high to low preference) to impute standard deviation values:

1. Standard deviation of change in blood pressure taken in a different position than that of the blood pressure data used
2. Standard deviation of blood pressure at the end of treatment
3. Standard deviation of blood pressure at the end of treatment measured in a different position than that of the blood pressure data used
4. Standard deviation of blood pressure at baseline (except if this measure is used for entry criteria)
5. Mean standard deviation of change in blood pressure from other trials using the same drug

Assessment of heterogeneity

Test for heterogeneity of treatment effect between the trials was made using a standard chi-square statistic for heterogeneity. The fixed-effect model was applied to obtain summary statistics of pooled trials, unless significant between-study heterogeneity was present, in which case the random-effects model was used.

Data synthesis

Data synthesis and analyses were carried out using the Cochrane Review Manager software, RevMan 5.3.

Data for changes in blood pressure and heart rate were combined using the mean difference with 95% confidence intervals (CIs). The WDAEs were analyzed using risk ratio. We planned to report risk difference, and number needed to treat or to harm when it was appropriate.

When the generic inverse variance method was used to incorporate cross-over trials into meta-analysis, the formula listed in *Cochrane Handbook for Systematic Reviews of Interventions*, section 16.4.6.1 (Higgins 2011) was used to calculate the standard deviation of difference between treatment and placebo. The standard error and sample sizes shown in the data analysis tables were unadjusted for subgroup comparison in order to minimize the loss of statistical power for the estimates. If necessary, the standard error would have been adjusted in dose-response analysis for studies containing multiple dosage subgroups in order to avoid double counting of patients.

Subgroup analysis and investigation of heterogeneity

If possible, we planned to include the following subgroup analyses.

1. Different regimens of the same active chemical entity
2. Gender, age and race
3. Co-morbid conditions: ischemic heart disease, peripheral vascular disease, diabetes
4. Baseline severity of hypertension: mild, moderate, or severe

Sensitivity analysis

We planned to test the robustness of the results using the following sensitivity analyses.

1. Trials that are industry-sponsored versus non-industry sponsored
2. Trials with blood pressure data measured in the sitting position versus other measurement positions
3. Trials with reported standard deviations of blood pressure change versus imputed standard deviations

RESULTS

Description of studies

Please refer to [Characteristics of included studies](#) and [Characteristics of excluded studies](#).

Results of the search

In order to save time and effort, a comprehensive search strategy ([Appendix 1](#); [Appendix 2](#); [Appendix 3](#); [Appendix 4](#)) was developed so that all four subclasses of beta blockers were searched simultaneously. All four beta blocker reviews ([Wong 2008 \(alpha and beta blockers\)](#); [Wong 2008 \(beta-1 blockers\)](#); [Wong 2014](#)) used the same study inclusion criteria. Citations were then sorted according to their respective subclasses afterward. Please refer to [Figure 1](#) for the flow of study selection. The search was first run in May 2010, and subsequent searches have been performed up to October 2014. A total of 22,195 citations were identified in all searches since May 2010, of which 8353 were confirmed to

be duplicates. The reviewers then screened 13,842 titles and abstracts, of which 13,229 citations were excluded. Six-hundred and thirteen citations were judged to potentially meet the inclusion criteria based on title and abstract. These were retrieved for detailed review. Four-hundred and eighty full text articles did not meet our inclusion criteria and were excluded. One citation was a separate publication of the same trial. One-hundred and thirty two trials met our inclusion criteria but 116 of them were excluded because they studied other subclasses of beta blockers, but not partial agonists. Three studies were excluded for reasons listed in the [Characteristics of excluded studies](#) table. Thirteen trials were included for the partial agonist review.

Figure 1. Study flow diagram

Included studies

Please refer to the [Characteristics of included studies](#) table for detailed descriptions of each included study. We included 13 studies examining the blood pressure lowering efficacy of six partial agonists in 612 hypertensive patients. Six hundred and five of 612 patients randomized to placebo or partial agonist mono therapy, completed the studies. Five of the 13 included studies were parallel studies and the other eight were cross-over studies. The duration of most of the included studies was four weeks. The average age of the participants was 52 and weighted mean baseline BP was 174.9/106.7 mmHg. Seven of the nine included studies that provided baseline BP had a baseline BP over 160/100 mmHg, therefore most of the patients included in these studies had moderate to severe hypertension. The baseline characteristic of partial agonist studies was different from the patient populations included in most trials in the other beta blocker reviews ([Wong 2008 \(alpha and beta blockers\)](#); [Wong 2008 \(beta-1 blockers\)](#); [Wong 2014](#)), which were mild hypertensive patients. Celiprolol was the most studied drug in this class with the largest

sample size. Only two of the 13 included studies specified the time (peak or trough) when BP was measured. [Vandongen 1986](#) measured BP at peak (zero to 12 hours after dose) and [Watson 1980](#) measured at trough (13 to 20 hours after dose). The medications were either taken multiple times a day or in the morning, therefore it should be reasonable to assume that most of the studies measured BP at peak hours.

Excluded studies

Please refer to [Characteristics of excluded studies](#) for detailed description of reasons for exclusion. Three studies that met the inclusion criteria were excluded from this review. The reasons for exclusion were lack of useful information (SBP and DBP data were not reported), adjustment of treatment according to BP and lack of randomization in the placebo group.

Risk of bias in included studies

[Figure 2](#) shows the 'Risk of bias' summary of each included study.

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Chalmers 1976	?	+	-	+	+
Chalmers 1982	+	+	-	+	+
Forette 1979	?	?	?	?	-
Hansson 1977	+	+	-	?	-
Moleur 1988	?	?	-	+	+
Motolese 1975	-	+	-	+	?
Olkinuora 2006	?	+	-	+	+
Salako 1979	?	+	-	+	+
Stumpe 1985	?	+	?	-	-
Tibblin 1969	?	+	?	+	?
Trafford 1989	?	+	?	+	+
Vandongen 1986	?	+	+	+	-
Watson 1980	?	+	-	?	-

Allocation

The procedure of randomization was poorly reported in most studies. We examined the baseline characteristics of each group in parallel studies. The baseline BP was significantly different in [Motolese 1975](#) between the groups. This raised the concern about selection bias. This issue was mentioned in the discussion. We did not find any reason to suspect that high risk of selection bias in any other studies. In cross-over studies, information was not sufficient to make any judgment on selection bias.

Blinding

Beta blockers generally lowered heart rate. For this reason, blinding could be compromised if the investigators had used mercury sphygmomanometer to measure blood pressure. Only one study used an automated machine which would mitigate the risk of detection bias ([Vandongen 1986](#)). The risk of detection bias remained high in this review.

Incomplete outcome data

Blood pressure and heart rate were reported by all the included studies. Due to the short duration of the studies, the dropout rate was low. Most of the patients randomized were included into the analyses. We judged that the risk of attrition bias was low.

Selective reporting

SBP and DBP were reported in all the included studies. They were reported as the end treatment values for each intervention group. Some of the studies did not report heart rate. The difference in the effect on heart rate compared to non-selective beta blockers could potentially distinguish partial agonists from other classes. Failure to report heart rate could be an indication of potential bias in reporting.

Although the dropout rate was low, only one study reported withdrawals due adverse effects (WDAEs). The overall subclass assessment of adverse effects serious enough to cause withdrawal could not be done due to lack of data. WDAE is an important outcome to assess drug tolerability, particularly in short-term studies. The selective reporting of WDAE raises concern about the risk of reporting bias.

Effects of interventions

See: [Summary of findings for the main comparison](#)

All results have been rounded up to whole number because it is not clinically meaningful to report blood pressure measure in two decimal places.

Acebutolol

Acebutolol is indicated for treatment of hypertension and ventricular arrhythmia in Canada ([eCPS](#)), the United States of America (USA) ([FDA](#)) and the European Union (EU) ([EMC](#)). The recommended dose for acebutolol in Canada to treat hypertension is 100 to 400 mg twice daily ([eCPS](#)).

Three studies examining the blood pressure lowering efficacy of acebutolol in 85 participants were included. [Forette 1979](#) and [Watson 1980](#) were cross-over studies, [Hansson 1977](#) was a parallel study. Only 400 mg/day acebutolol was studied with a treatment duration ranging from four to eight weeks. The mean baseline BP for acebutolol studies was 176/113 mmHg.

Please refer to [Analysis 1.1](#) to [Analysis 1.4](#) for results of acebutolol. Based on available data, acebutolol 400 mg/day lowered SBP by -5 mmHg [95% CI, -9 to -1], but did not significantly lower DBP compared to placebo (-2 mmHg [95% CI, -4 to 0]). Acebutolol 400 mg/day lowered heart rate by -9 BPM [-11 to -7] compared to placebo but did not significantly change pulse pressure (-2 mmHg [95% CI, -5 to 1]).

Pindolol

Pindolol is indicated for treatment of hypertension and angina pectoris in Canada and the EU ([eCPS](#); [EMC](#)), and only for hypertension in the USA ([FDA](#)). The recommended dose for pindolol in Canada to treat hypertension is 5 mg twice daily to 15 mg three times daily ([eCPS](#)). Three studies examining blood pressure lowering efficacy of 10 and 30 mg/day pindolol in 50 hypertensive patients were included. Forty-five of 50 randomized patients completed the studies. All of the pindolol studies were cross-over studies with a duration ranging from three to eight weeks. Only one study provided baseline DBP information, which was 93 mmHg. Please refer to [Analysis 2.1](#) to [Analysis 2.4](#) for results of pindolol. Pindolol 10 mg/day significantly lowered SBP (-14 mmHg [95% CI, -20 to -9]), DBP (-7 mmHg [95% CI, -10 to -4]) and heart rate (-6 BPM [95% CI, -10 to -2]) compared to placebo. At 30 mg/day, pindolol significantly lowered SBP (-13 mmHg [95% CI, -20 to -5]) and DBP (-9 mmHg [95% CI, -15 to -3]). Heart rate was not reported for 30 mg/day. Indirect comparison did not find any significant difference in SBP and DBP between 10 mg/day and 30 mg/day pindolol. Pindolol 10 mg/day significantly lowered pulse pressure compared to placebo. However, 30 mg/day pindolol did not significantly change pulse pressure.

Celiprolol

Celiprolol is indicated for treatment of hypertension in the EU. It is not available in Canada or the USA. The recommended dose for celiprolol to treat hypertension is 200 to 400 mg once daily

(EMC). Three studies examining the blood pressure lowering efficacy of 200 to 600 mg/day celiprolol in 267 hypertensive patients were included in this analysis. Two of the randomised controlled trials were parallel studies and the other one was a cross-over study. These studies had a duration ranging from four to 12 weeks. Mean baseline BP for the celiprolol studies was 163/100 mmHg. Please refer to [Analysis 3.1](#) to [Analysis 3.4](#) for celiprolol results. All three doses of celiprolol significantly lowered both SBP and DBP compared to placebo. Celiprolol 200 mg/day, which contained the largest sample size, lowered SBP by -8 mmHg [95% CI, -12 to -4] and DBP by -5 mmHg [95% CI, -7 to -3]. The direct comparisons of dose effect did not find a significant difference between 200 mg/day and 400 mg/day in both SBP and DBP ([Analysis 3.5](#); [Analysis 3.6](#)). The overlapping 95% CIs are consistent with such findings. [Trafford 1989](#) was the only study that reported information on heart rate in celiprolol. Celiprolol 200 mg/day and 400 mg/day did not significantly lowered heart rate compared to placebo. Celiprolol 200 mg/day was the only subgroup that significantly lowered pulse pressure compared to placebo.

Alprenolol

Alprenolol is not available in Canada, the USA or the EU. We did not find the product monograph from these government agencies, therefore we were unable to provide the indication and recommended dosage for alprenolol. Two studies examining the blood pressure lowering efficacy of 400 mg/day alprenolol in 27 hypertensive patients were included in this analysis. Both of the studies were cross-over studies with a duration ranging from eight to 10 weeks. Alprenolol 400 mg/day significantly lowered SBP (-17 mmHg [95% CI, -24 to -10]), DBP (-7 mmHg [95% CI, -10 to -3]), heart rate (-8 BPM [95% CI, -15 to -1]) and pulse pressure (-9 mmHg [95% CI, -15 to -3]) compared to placebo. Please refer to [Analysis 4.1](#) to [Analysis 4.4](#) for alprenolol results.

Bopindolol

Bopindolol is not available in Canada, the USA or the EU. We did not find the product monograph of bopindolol from any government agencies therefore we cannot provide the indication and recommended dosage for bopindolol. Bopindolol is a prodrug of pindolol with an ester. One parallel study examining blood pressure lowering efficacy of 0.5 to 2 mg once daily bopindolol for four weeks in 117 hypertensive patients was included in this review. A hundred and fifteen out of 117 randomized patients completed the study.

Please refer to [Analysis 5.1](#) to [Analysis 5.4](#) for bopindolol hemodynamic results. Bopindolol, in all doses, did not significantly lower SBP or DBP compared to placebo. Bopindolol 1 mg/day and 2 mg/day significantly lowered heart rate compared to placebo. Bopindolol did not significantly change pulse pressure compared to placebo in all doses tested.

Withdrawal due to adverse effects (WDAE)

[Moleur 1988](#) was the only study that reported usable WDAE data in this review. Bopindolol was not significantly different from placebo in terms of WDAE (RR 0.72 [0.07, 7.67]) ([Analysis 5.5](#)).

Oxprenolol

Oxprenolol is not available in Canada, the USA or the EU. It was indicated for the treatment of hypertension in the EU. When it was available in the EU, the recommended dose of oxprenolol for treatment of hypertension was 80 to 320 mg once daily (EMC). One parallel study examining blood pressure lowering efficacy of 20 to 80 mg once daily oxprenolol in 66 hypertensive patients for four weeks was included in this review.

Please refer to [Analysis 6.1](#) to [Analysis 6.2](#) for oxprenolol hemodynamic results. Oxprenolol at 60 and 80 mg/day (the starting dose) significantly lowered SBP (-12 mmHg [95% CI, -22 to -1]) compared to placebo. No other doses of the oxprenolol significantly lowered SBP or DBP compared to placebo. [Motolese 1975](#) did not report any data on heart rate. Oxprenolol did not significantly change pulse pressure in any dose subgroup.

Pooled effects of partial agonists

We pooled the results of partial agonists based on the manufacturer's recommended starting doses ([Analysis 7.1](#); [Analysis 7.2](#); [Analysis 7.3](#); [Analysis 7.4](#)). This allowed us to analyze the effects of partial agonists as a whole subclass. [Summary of findings for the main comparison](#) summarizes the overall results in SBP, DBP, heart rate and pulse pressure.

Partial agonists in 0.25x and 0.5x starting dose contained little data and generally did not significantly lower SBP or DBP compared to placebo, although the 0.5x starting dose subgroup showed a marginally significant result. Starting from the recommended starting dose, partial agonists significantly lowered SBP and DBP compared to placebo. Test for subgroup differences within the recommended dose range (1x, 2x and 4x the starting dose) by the direct comparison method was not significant for SBP ($P = 0.84$) or DBP ($P = 0.74$). This suggested that higher-dose partial agonists did not offer greater BP lowering effect compared to the recommended starting dose of partial agonists. When we combined the starting dose and twice the starting dose subgroups ([Analysis 7.6](#)), partial agonists lowered SBP by 8 mmHg [95% CI, -10 to -6] and DBP by 4 mmHg [95% CI, -5 to -3].

The recommended starting dose of partial agonists was the only dose that significantly lowered heart rate compared to placebo. Test for subgroup differences for heart rate using a direct comparison method was not significant. We calculated the pulse pressure by subtracting DBP from SBP. Partial agonists at starting and 2x starting doses significantly lowered pulse pressure. The combined effect of starting and twice starting dose for pulse pressure was -4 mmHg [95% CI, -5 to -2]; 4x starting dose subgroup showed

similar point estimate but the 95% CI was wide and not statistically significant.

Only one study (bopindolol) reported WDAE (Moleur 1988). Bopindolol was not significantly different compared to placebo in terms of WDAE. It is a small study with 117 patients taking beta blockers for four weeks. We did not find any data on WDAE for other partial agonists.

Blood pressure variability

We tested the BP variability by paired t-test comparing the standard deviations of the partial agonist group and the placebo group. The average end treatment standard deviation of SBP in partial agonist group was 16.3 and in placebo group was 14.8. The average SD of DBP for the treatment group was 8.4 and placebo group was also 8.4. The P value for the paired t-test for SBP was 0.02 and for DBP was 0.64. The results suggested that partial agonists might increase the variability of SBP but not DBP. We only included a small sample of nine end-treatment standard deviations for each group. Therefore, more data are needed in order to answer this question.

Subgroup and sensitivity analysis

Due to lack of data and small sample size, we were not able to perform any of the subgroup or sensitivity analyses.

DISCUSSION

Summary of main results

Celiprolol was the most studied partial agonist in this review. The blood pressure (BP) and heart rate lowering profile of celiprolol reflected the effects that were expected from a partial agonist. Celiprolol significantly lowered SBP and DBP compared to placebo while having no significant effect on heart rate. We did not find a significant dose-response effect between celiprolol 200 mg/day and 400 mg/day. This suggested that 400 mg/day celiprolol did not lower blood pressure more than the 200 mg/day celiprolol. Motolese 1975 was the only study included in oxprenolol analyses. The baseline of the 60 and 80 mg/day subgroups (188/112 mmHg) were much higher than placebo (175/109 mmHg). The unbalanced baseline BP raised concerns for the adequacy of randomization. Since no other oxprenolol subgroup significantly lowered BP and the risk of selection bias was high in this subgroup, the effect in the 60 and 80 mg/day subgroup could be an exaggeration. This subgroup only had a small sample size and did not significantly affect the overall pooled results.

The sample sizes of other partial agonists were too small to draw any definitive conclusion. It is troubling that acebutolol and pindolol, which are approved in Canada and the USA to treat hypertension, provided little publicly available data.

Overall subclass effect of partial agonists

The mean baseline BP of partial agonists studies (175/107 mmHg) was higher than the other classes of beta blockers. The patients enrolled in the studies generally had moderate to severe hypertension. Most of the studies were published back in the 1970s and 1980s. The definition of hypertension at that time was >160/100 mmHg.

Only two of the 13 included studies specified whether BP was measured at peak (one to 12 hours after dose) or trough hours (13 to 24 hours after dose). However, the fact that many of the partial agonists used in the studies were taken two to three times a day, it is reasonable to assume that BP was measured at peak hours in these studies.

In the pooled data, 0.25 and 0.5 times the recommended starting dose did not significantly lower SBP or DBP. The recommended starting dose and higher doses significantly lowered both SBP and DBP. Direct comparison showed no significant difference in BP lowering effect between the starting dose and higher doses. The 1x and 2x starting dose subgroups contained the largest sample size. The estimate of BP lowering efficacy for partial agonists by combining the 1x and 2x starting dose subgroup was -8/-4 mmHg.

Heart rate

The combined effects of 1x and 2x starting dose subgroups on heart rate for partial agonist (-5 beats per minute) was smaller than non-selective beta blockers (-9 beats per minute). This result suggests that partial agonists might be less likely to cause bradycardia than other non-selective beta blockers.

The rationale of developing partial agonists was that by having agonistic properties, partial agonists could produce fewer side effects of beta antagonism, such as bradycardia, fatigue, and rebound hypertension after withdrawal. The available data did not answer whether this was the case as many trials did not report the effect on heart rate or withdrawals due to adverse effects (WDAEs).

Pulse pressure

Partial agonists significantly lowered pulse pressure compared to placebo. The relatively small effect on DBP could help explain why partial agonist, with smaller sample size, was the only beta blocker subclass that showed an effect on pulse pressure of this magnitude. The agonistic property of partial agonists on peripheral beta-2 receptors, causing vasodilation and improving blood vessel compliance, could lower pulse pressure and offer another explanation for this finding.

BP variability

In this review, we found that the SBP end treatment standard deviation of partial agonists was significantly higher compared to placebo. Due to the small sample size it was difficult to draw a definitive conclusion. Only six of 13 studies provided the end treatment standard deviations in the partial agonist and placebo groups. Attempts to contact the authors in order to obtain this information were not successful. In addition, measuring BP at peak hours might increase BP variability. It was possible that the higher variability in SBP might disappear when BP was measured at trough hours. Large, well-conducted studies comparing the BP variability of partial agonists and placebo are needed in order to shed more light on this matter.

Compared to other classes of drugs

Based on an informal indirect comparison of peak BP lowering effects observed in other Cochrane reviews on angiotensin-converting-enzyme (ACE) inhibitors (-11/-6 mm Hg) and ARBs (-12/-7 mmHg) compared with placebo (Heran 2008 (ACEI); Heran 2008 (ARB)), which used similar inclusion/exclusion criteria to the present review, partial agonist (-8/-4 mmHg) lowered peak BP by a smaller magnitude. The estimate of the effect of partial agonists on pulse pressure was larger at 4 mmHg than other beta blockers, but because of the very low quality of the evidence more studies are needed to know whether partial agonists have a different effect on pulse pressure than other subclasses of beta blockers. The baseline BP in trials of partial agonists (175/107 mmHg) was much higher than ACE inhibitors (157/101 mmHg) and ARBs (156/101 mmHg). The absolute amount of reduction of BP is expected to be higher when the baseline BP is higher. Therefore, it is likely that the trough BP lowering effect of partial agonists in a mild hypertensive population would be smaller than the current estimate.

Overall completeness and applicability of evidence

This review represents the best evidence available for the blood pressure lowering efficacy of partial agonist beta blockers. The objectives of the included studies were similar to our review. The participants of these trials were middle-aged, primary hypertensive patients. The average baseline blood pressures were mostly in the moderately elevated range and most of the trials were performed in the 1970's and 1980's.

Quality of the evidence

Summary of findings for the main comparison summarizes the combined effect size of the combined starting and 2x the starting dose of partial agonists. In addition, it provides a judgment of the

quality of evidence in this review. Included in this review were 13 studies examining the BP lowering effect of partial agonists in 605 middle age hypertensive patients. The average baseline blood pressures were mostly in the severely elevated range.

Only one study used an automated machine to measure blood pressure. This suggests that the risk of detection bias is high due to loss of blinding in this review. Because of the high risk of detection bias, the quality of evidence was downgraded by one level.

Due to the small sample size of this review, the estimates are likely to change when additional data are made available in the future. This is the reason that the quality of evidence was downgraded by another level.

In addition, a search for acebutolol and pindolol trials, which are approved for treatment of hypertension in North America, had yielded only a small amount of data. This raises suspicion that large trials required to achieve licensing have not been published. Therefore, the risk of publication bias in this review is high, which downgraded the quality of evidence by another level.

For these reasons, the estimates of the BP lowering effect shown in the 'Summary of findings' table are very likely an exaggeration of the true effect. This is reflected in the table by the very low judgment of the quality of the evidence.

Potential biases in the review process

The rigid inclusion criteria of this review minimized potential bias during the review process. The inclusion of the studies was based strictly on the methodology of the studies, the results of the studies paid no role in the decision. The duty of the review authors were solely to determine whether the methodology had met the inclusion criteria. Therefore, we were confident that the risk of bias during review process was very low.

Agreements and disagreements with other studies or reviews

Two other reviews, Chen 2010 and Law 2005, assessed the blood pressure lowering efficacy of beta blockers. However, these two reviews pooled the results of different classes of beta blockers together as one large class. We believe that this could be problematic as different classes of beta blockers, which have differences in mechanism of action, could have different effects on blood pressure. Pooling the data together could lead to misrepresentation of the effect of individual beta blockers. Therefore, it was inappropriate to compare the results of this review to these previously published reviews.

AUTHORS' CONCLUSIONS

Implications for practice

This review provides the best estimate of the blood pressure lowering efficacy of six partial agonists. In patients with moderate to severe hypertension, there was very low quality evidence that partial agonists lowered peak BP by an average of 8/4 mmHg and reduced heart rate by five beats per minute. The maximum BP lowering effect of partial agonists was shown at the recommended starting dose. There was no evidence of greater effect at doses higher than the starting doses. Based on the indirect comparison of the results in this review and the Cochrane reviews on non-selective and beta-1 selective blockers, ACE inhibitors and ARBs, the BP lowering effect appeared to be less than non-selective and beta-1 selective blockers in comparable trials and less than the peak effect of ACE inhibitors and angiotensin receptor blockers (ARBs) in patients with mild to moderate elevations in BP.

Partial agonists did not show a convincing dose-response effect on heart rate. Higher dose partial agonists decreased heart rate to a lesser degree. Partial agonists were the only subclass of beta blockers that did not show a convincing dose-response on heart rate. Starting from the recommended dose, partial agonists consistently lowered pulse pressure. The magnitude of pulse pressure reduction was 3 to 4 mmHg and similar for all doses.

Implications for research

As shown in this review, the sample size of available trials was small. Many trials must have been conducted to satisfy regulatory authorities that are at present unavailable. The data from these trials must be made available. Even when this is done it is likely that more large randomized controlled trials will be needed in order to better assess the dose-related blood pressure lowering efficacy of partial agonist beta blockers. In order to minimize bias, future randomized controlled trials should:

1. Contain detailed descriptions of the method of randomization and allocation of concealment procedures.
2. Use automated machines for BP measurement to reduce loss of blinding bias.
3. Measure BP and heart rate at both peak and trough hour.
4. Report withdrawals due to adverse effects.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Chalmers 1976

Methods	Randomized double-blinded placebo-controlled cross-over study with 8 week treatment periods	
Participants	N = 21, 16 completed the study.Baseline DBP 95 to 120 mmHg, age 30 to 60, primary hypertension and not COPD, unstable hypertension, retinopathy or diabetes	
Interventions	Pindolol 10 mg three times per day, Hydrochlorothiazide 50 mg once daily, combination of the two, placebo	
Outcomes	Sitting, supine standing SBP, DBP, HR, lab, ECG, Chest x-ray, side effects	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information.
Allocation concealment (selection bias)	Low risk	Placebo for hydrochlorothiazide and pindolol were used.
Blinding (performance bias and detection bias) All outcomes	High risk	Did not use automated machine. Blinding might be compromised due to lower HR
Incomplete outcome data (attrition bias)	Low risk	Dropouts were reported and not included in analysis.
Selective reporting (reporting bias)	Low risk	All outcomes reported.

Chalmers 1982

Methods	Randomized double-blinded placebo-controlled cross-over study with eight-week washout and four eight-week treatment periods	
Participants	Mean age 53 ± 10, 7 men 9 women, with supine DBP between 95 mmHg to 120 mmHg	
Interventions	Pindolol 5 mg twice daily, indapamide 2.5 mg once daily, indapamide and pindolol combo, placebo	

Chalmers 1982 (Continued)

Outcomes	Sitting, standing, supine SBP, DBP, HR, plasma renin and aldosterone, plasma K, Cl, HCO3-, urate, WDAE	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence determined by Latin square. Baseline DBP showed no significant different between periods
Allocation concealment (selection bias)	Low risk	Placebo was used for both indapamide and pindolol.
Blinding (performance bias and detection bias) All outcomes	High risk	Mercury sphygmomanometer was used, there was a chance that blinding could be compromised due to a lower HR by pindolol
Incomplete outcome data (attrition bias)	Low risk	All hemodynamic outcomes reported without dropouts.
Selective reporting (reporting bias)	Low risk	Non suspected.

Forette 1979

Methods	Randomized double-blinded placebo-controlled cross-over study with 10-week treatment phase. 8 weeks on fixed dose then 2-week titration down period	
Participants	n = 34, all participants were female, mean age 81 with SBP >160 mmHg and DBP > 90 mmHg. Exclusion: renal insufficiency, HR < 50, Heart failure, AV block, asthma	
Interventions	Acebutolol 200 mg twice daily, diuretic/acebutolol combination, placebo	
Outcomes	SBP, DBP, HR, serum drug level, plasma renin activity.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information.

Forette 1979 (Continued)

Allocation concealment (selection bias)	Unclear risk	No information.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Device used to measure BP was unknown.
Incomplete outcome data (attrition bias)	Unclear risk	No information.
Selective reporting (reporting bias)	High risk	WDAEs were not reported.

Hansson 1977

Methods	Randomized double-blinded placebo-controlled parallel study, with 12-week treatment period
Participants	n = 38, Patients with primary hypertension, average age 55.6, baseline average BP 177/106
Interventions	Acebutolol 400 mg, 600 mg, 1200 mg once daily with cross-over style at 4 weeks each. Placebos were given for whole 12-week period
Outcomes	SBP, DBP, HR, side effects.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The baseline for both groups were similar.
Allocation concealment (selection bias)	Low risk	Placebo was given at the same frequency as treatment.
Blinding (performance bias and detection bias) All outcomes	High risk	Did not use automated machine. Blinding might be compromised due to lowered HR
Incomplete outcome data (attrition bias)	Unclear risk	No information on dropouts.
Selective reporting (reporting bias)	High risk	Did not report WDAE.

Moleur 1988

Methods	Randomized double-blinded parallel group placebo-controlled 4 weeks duration	
Participants	n = 117, 115 completed. Supine DBP between 90 to 114 mmHg at the end of run in period, excluded pregnancy and lactation, secondary hypertension	
Interventions	Bopindolol 0.5 mg, 1 mg and 2 mg once daily, placebo.	
Outcomes	SBP, DBP, HR, symptom questionnaire.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information.
Allocation concealment (selection bias)	Unclear risk	No information.
Blinding (performance bias and detection bias) All outcomes	High risk	Mercury sphygmomanometer was used. Blinding could be compromised due to lower heart rate
Incomplete outcome data (attrition bias)	Low risk	The study was presented as ITT, two people lost to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes reported.

Motolese 1975

Methods	Randomized double-blinded parallel placebo-controlled study with duration of 4 weeks	
Participants	n = 329, baseline BP 189.5/113.3 mmHg. Patients age < 65, with SBP < 250 mmHg and DBP between 100 and 130 mmHg. Excluded HF, asthma, bradycardia, AV conduction defect, retinopathy, blood urea nitrogen exceeding 50 mg/ 100 ml, serum creatinine greater than 1.5 mg/100 mL	
Interventions	Oxprenolol 20, 40, 60, 80 mg once daily or combination with hydrochlorothiazide or dihydralazine, placebo	
Outcomes	WDAE, supine and standing SBP, DBP, lab.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Motolese 1975 (Continued)

Random sequence generation (selection bias)	High risk	The baseline BP of 60 and 80 mg/day groups are much higher than placebo
Allocation concealment (selection bias)	Low risk	"All the trial medications, including placebo, were prepared by the manufacturer in identical capsules."
Blinding (performance bias and detection bias) All outcomes	High risk	Mercury sphygmomanometer were used. Blinding could be compromised by lowered HR
Incomplete outcome data (attrition bias)	Low risk	Dropouts were reported and accounted for.
Selective reporting (reporting bias)	Unclear risk	Did not describe outcomes in the methods.

Olkinuora 2006

Methods	Randomized double-blind placebo-controlled parallel study for 3 months
Participants	Total n = 112, 56 randomized to beta blocker mono therapy or placebo, baseline BP 159.5/94 mmHg, average age 61, with systolic hypertension defined as SBP > 140 mmHg. Exclusion BMI > 35, CHD, LVH, unstable asthma, newly diagnosed type 2 diabetes, total serum cholesterol level > 9 mmol/L or SBP > 180 mmHg
Interventions	Celiprolol 200 mg once daily, simvastatin 10 mg once daily, combination of the two once daily, placebo
Outcomes	SBP, DBP, total cholesterol, LDL, HDL, TG.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information.
Allocation concealment (selection bias)	Low risk	Double dummy was used.
Blinding (performance bias and detection bias) All outcomes	High risk	Did not use automated machine.
Incomplete outcome data (attrition bias)	Low risk	All hemodynamic data reported, all patients accounted for.

Olkinuora 2006 (Continued)

Selective reporting (reporting bias)	Low risk	All outcomes reported.
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Salako 1979

Methods	Randomized double-blinded placebo-controlled cross-over study with 8-week treatment period
Participants	n = 16, pre-treatment DBP between 95 to 120 mmHg. Patients had previously been treated with antihypertensive for 1 to 9 years. Exclusion: renal, liver disease, diabetes
Interventions	Alprenolol 200 mg twice daily, placebo.
Outcomes	SBP, DBP, HR, serum level, side effects, WDAE.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information regarding procedure.
Allocation concealment (selection bias)	Low risk	Placebo with same frequency was given.
Blinding (performance bias and detection bias) All outcomes	High risk	Automated machine was not used. Blinding might be compromised due to lower HR
Incomplete outcome data (attrition bias)	Low risk	Withdrawal patients were not included in the analysis.
Selective reporting (reporting bias)	Low risk	All outcome reported.

Stumpe 1985

Methods	Randomized double-blind placebo-controlled parallel study for 4 weeks
Participants	n = 232, 185 randomized to partial agonist mono therapy or placebo. Participants with supine DBP between 95 to 114 mmHg during the washout period. Baseline BP 165/102 mmHg
Interventions	Celiprolol 200 mg, 400 mg, 600 mg, atenolol 50 mg once daily, placebo
Outcomes	Supine SBP, DBP, HR.

Stumpe 1985 (Continued)

Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Low risk	All patients took 3 tablets once daily, the content of the tablets were determined by the assigned treatment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias)	High risk	SBP, DBP, HR reported without SD or SEM
Selective reporting (reporting bias)	High risk	Dropout was not reported.

Tibblin 1969

Methods	Randomized double-blinded placebo-controlled cross-over study with two 12-week treatment periods	
Participants	n = 11, baseline BP 179/115 mmHg. Patients with supine SBP > 150 mmHg, and supine DBP > 100 mmHg. Exclusion asthma, chronic bronchitis, heart failure, retinopathy or renal hypertension	
Interventions	Alprenolol 100 mg four times a day, placebo.	
Outcomes	Sitting, standing, supine SBP, DBP, blood and urine lab.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information.
Allocation concealment (selection bias)	Low risk	Placebo tablets were given at same frequency as active treatment

Tibblin 1969 (Continued)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information regarding measuring device.
Incomplete outcome data (attrition bias)	Low risk	All hemodynamic outcomes reported.
Selective reporting (reporting bias)	Unclear risk	Study reported no side effects except for 1, it is unclear how these data are related to WDAEs

Trafford 1989

Methods	After single blind run in period, patients entered a randomized double-blinded 3-way cross-over study with 4-week treatment periods
Participants	n = 26, age 20-65, sitting DBP between 94 to 116 mmHg during the 4 week run in period. Exclusion: DBP > 120 mmHg, malignant or labile hypertension, MI, heart failure, sinus bradycardia, 2nd or 3rd degree heart block, arrhythmia, COPD, insulin-dependent diabetes, uncontrolled renal, hepatic, GI, endocrine diseases, contraindicated for beta blockers
Interventions	Celiprolol 200 mg once daily, 400 mg once daily and placebo.
Outcomes	Sitting SBP, DBP, HR, blood, clinical chemistry, liver function, urinalysis
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information.
Allocation concealment (selection bias)	Low risk	Placebo was used with the same frequency as treatment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information on measuring device.
Incomplete outcome data (attrition bias)	Low risk	No patients withdrew.
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported.

Vandongen 1986

Methods	Randomized double-blinded placebo-controlled cross-over study with no washout and 3-week treatment periods	
Participants	Age 29-65, 10 men 3 women, with primary hypertension.	
Interventions	Pindolol 5 mg twice daily, metoprolol 100 mg twice daily, placebo	
Outcomes	Resting peak SBP, DBP, HR, post exercise SBP, DBP, HR, plasma noradrenaline and adrenaline	
Notes	Baseline information of patients was not given.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study stated order of treatment was random. No information regarding procedure
Allocation concealment (selection bias)	Low risk	“capsules were identical”
Blinding (performance bias and detection bias) All outcomes	Low risk	The assessments were done by automatic machines. Investigators could not determine the treatment based on HR
Incomplete outcome data (attrition bias)	Low risk	All hemodynamic outcomes were reported.
Selective reporting (reporting bias)	High risk	Withdrawals due to adverse effect were not reported.

Watson 1980

Methods	Randomized double-blinded placebo-controlled cross-over study with 4-week washout and three 4-week treatment periods	
Participants	n = 13, patients with BP greater than 150/100 mmHg were enrolled. Exclusion: organ damage or asthma	
Interventions	Placebo twice daily, Acebutolol 400 once daily, Acebutolol 200 mg twice daily	
Outcomes	Resting trough SBP, DBP, HR, serum drug levels.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Watson 1980 (Continued)

Random sequence generation (selection bias)	Unclear risk	No information.
Allocation concealment (selection bias)	Low risk	Placebo was used to conceal the frequency of treatment.
Blinding (performance bias and detection bias) All outcomes	High risk	Automatic machine not used for measurement, blinding might be compromised due to lower HR
Incomplete outcome data (attrition bias)	Unclear risk	SBP, DBP, HR reported. Did not mention dropouts.
Selective reporting (reporting bias)	High risk	WDAE was not reported.

BMI: body mass index

CHD: coronary heart disease

Cl: chloride

COPD: chronic obstructive pulmonary disease

DBP: diastolic blood pressure

ECG: electrocardiogram

GI: gastrointestinal

HD: heart failure

HDL: high-density lipoprotein

HR: heart rate

ITT: intention-to-treat

K: plasma potassium

lab: laboratory tests

LDL: low-density lipoprotein

LVH: left ventricular hypertrophy

MI: myocardial infarction

SBP: systolic blood pressure

SD: standard deviation

SEM: standard error of the mean

TG: triglyceride

WDAE: withdrawal due to adverse event

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Erley 1997	Only reported MAP. SBP and DBP data were not reported.
Fraser 1986	If BP was not adequately controlled at any stage, prazosin was added in standard dosage

(Continued)

Lewis 1984	The placebo period was place between treatment periods. Therefore, the time to give placebo was not in random order
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BP: blood pressure

DBP: diastolic blood pressure

MAP: mean arterial pressure

SBP: systolic blood pressure

DATA AND ANALYSES

Comparison 1. Acebutolol vs Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SBP	3		Mean Difference (Fixed, 95% CI)	Subtotals only
1.1 (starting dose) 400mg/day	3	85	Mean Difference (Fixed, 95% CI)	-5.12 [-8.85, -1.40]
2 DBP	3		Mean Difference (Fixed, 95% CI)	Subtotals only
2.1 (starting dose) 400mg/day	3	85	Mean Difference (Fixed, 95% CI)	-1.77 [-3.88, 0.34]
3 Heart rate	3		Mean Difference (Fixed, 95% CI)	Subtotals only
3.1 (starting dose) 400mg/day	3	85	Mean Difference (Fixed, 95% CI)	-8.68 [-10.85, -6.51]
4 Pulse pressure	3		Mean Difference (Fixed, 95% CI)	Subtotals only
4.1 (starting dose) 400 mg/day	3	85	Mean Difference (Fixed, 95% CI)	-2.40 [-5.39, 0.59]

Comparison 2. Pindolol vs Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SBP	3		Mean Difference (Fixed, 95% CI)	Subtotals only
1.1 (starting dose) 10 mg/day	2	29	Mean Difference (Fixed, 95% CI)	-14.46 [-19.84, -9.08]
1.2 (4x starting) 30 mg/day	1	16	Mean Difference (Fixed, 95% CI)	-12.5 [-20.16, -4.84]
2 DBP	3		Mean Difference (Fixed, 95% CI)	Subtotals only
2.1 (starting dose) 10 mg/day	2	29	Mean Difference (Fixed, 95% CI)	-6.88 [-10.15, -3.61]
2.2 (4x starting) 30 mg/day	1	16	Mean Difference (Fixed, 95% CI)	-8.8 [-14.80, -2.80]
3 Heart rate	2		Mean Difference (Fixed, 95% CI)	Subtotals only
3.1 (starting dose) 10 mg/day	2	29	Mean Difference (Fixed, 95% CI)	-5.91 [-9.50, -2.32]
4 Pulse pressure	3		Mean Difference (Fixed, 95% CI)	Subtotals only
4.1 (starting dose) 10 mg/day	2	29	Mean Difference (Fixed, 95% CI)	-8.01 [-12.74, -3.29]
4.2 (4x starting) 30 mg/day	1	16	Mean Difference (Fixed, 95% CI)	-3.70 [-10.34, 2.94]

Comparison 3. Celiprolol vs Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SBP	3		Mean Difference (Fixed, 95% CI)	Subtotals only
1.1 (starting dose) 200 mg/day	3	171	Mean Difference (Fixed, 95% CI)	-7.86 [-11.88, -3.84]
1.2 (2x starting) 400 mg/day	2	120	Mean Difference (Fixed, 95% CI)	-8.59 [-13.41, -3.77]
1.3 (4x starting) 600 mg/day	1	90	Mean Difference (Fixed, 95% CI)	-10.0 [-16.47, -3.53]

2 DBP	3		Mean Difference (Fixed, 95% CI)	Subtotals only
2.1 (starting dose) 200 mg/day	3	171	Mean Difference (Fixed, 95% CI)	-4.57 [-6.62, -2.53]
2.2 (2x starting) 400 mg/day	2	120	Mean Difference (Fixed, 95% CI)	-4.88 [-7.25, -2.52]
2.3 (4x starting) 600 mg/day	1	90	Mean Difference (Fixed, 95% CI)	-6.0 [-9.49, -2.51]
3 Heart rate	1		Mean Difference (Fixed, 95% CI)	Subtotals only
3.1 (starting dose) 200 mg/day	1	26	Mean Difference (Fixed, 95% CI)	-2.4 [-4.93, 0.13]
3.2 (2x starting) 400 mg/day	1	26	Mean Difference (Fixed, 95% CI)	-0.6 [-3.36, 2.16]
4 Pulse pressure	3		Mean Difference (Fixed, 95% CI)	Subtotals only
4.1 (starting dose) 200 mg/day	3	171	Mean Difference (Fixed, 95% CI)	-3.76 [-7.26, -0.25]
4.2 (2x starting) 400 mg/day	2	120	Mean Difference (Fixed, 95% CI)	-3.89 [-8.09, 0.32]
4.3 (4x starting) 600 mg/day	1	90	Mean Difference (Fixed, 95% CI)	-4.0 [-9.59, 1.59]
5 SBP dose comparison	2		Mean Difference (Fixed, 95% CI)	Subtotals only
5.1 200 mg/day	2	80	Mean Difference (Fixed, 95% CI)	-7.42 [-12.15, -2.69]
5.2 400 mg/day	2	85	Mean Difference (Fixed, 95% CI)	-8.59 [-13.41, -3.77]
6 DBP dose comparison	2		Mean Difference (Fixed, 95% CI)	Subtotals only
6.1 200 mg/day	2	80	Mean Difference (Fixed, 95% CI)	-5.09 [-7.34, -2.85]
6.2 400 mg/day	2	85	Mean Difference (Fixed, 95% CI)	-4.88 [-7.25, -2.52]

Comparison 4. Alprenolol vs Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SBP	2		Mean Difference (Fixed, 95% CI)	Subtotals only
1.1 400 mg/day	2	27	Mean Difference (Fixed, 95% CI)	-16.94 [-23.86, -10.01]
2 DBP	2		Mean Difference (Fixed, 95% CI)	Subtotals only
2.1 400 mg/day	2	27	Mean Difference (Fixed, 95% CI)	-6.73 [-10.06, -3.39]
3 Heart rate	1		Mean Difference (Fixed, 95% CI)	Subtotals only
3.1 400 mg/day	1	16	Mean Difference (Fixed, 95% CI)	-8.0 [-15.45, -0.55]
4 Pulse pressure	2		Mean Difference (Fixed, 95% CI)	Subtotals only
4.1 400 mg/day	2	27	Mean Difference (Fixed, 95% CI)	-8.71 [-14.77, -2.65]

Comparison 5. Bopindolol vs Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SBP	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 0.5 mg/day	1	55	Mean Difference (IV, Fixed, 95% CI)	-5.90 [-15.77, 3.97]
1.2 1 mg/day	1	60	Mean Difference (IV, Fixed, 95% CI)	-6.10 [-15.58, 3.38]
1.3 2 mg/day	1	60	Mean Difference (IV, Fixed, 95% CI)	-5.80 [-14.64, 3.04]
2 DBP	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 0.5 mg/day	1	55	Mean Difference (IV, Fixed, 95% CI)	-1.5 [-6.84, 3.84]

2.2 1 mg/day	1	60	Mean Difference (IV, Fixed, 95% CI)	-4.0 [-9.05, 1.05]
2.3 2 mg/day	1	60	Mean Difference (IV, Fixed, 95% CI)	-2.40 [-7.24, 2.44]
3 Heart rate	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 0.5 mg/day	1	55	Mean Difference (IV, Fixed, 95% CI)	-2.23 [-7.33, 2.87]
3.2 1 mg/day	1	60	Mean Difference (IV, Fixed, 95% CI)	-5.57 [-10.13, -1.01]
3.3 2 mg/day	1	60	Mean Difference (IV, Fixed, 95% CI)	-6.06 [-10.21, -1.91]
4 Pulse pressure	1		Mean Difference (Fixed, 95% CI)	Subtotals only
4.1 0.5 mg/day	1	55	Mean Difference (Fixed, 95% CI)	-4.8 [-13.35, 3.75]
4.2 1 mg/day	1	60	Mean Difference (Fixed, 95% CI)	-2.1 [-10.39, 6.19]
4.3 2 mg/day	1	60	Mean Difference (Fixed, 95% CI)	-3.4 [-11.06, 4.26]
5 WDAE	1	117	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.07, 7.67]

Comparison 6. Oxprenolol vs Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SBP	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 (0.25x starting) 20 mg/day	1	26	Mean Difference (IV, Fixed, 95% CI)	3.40 [-8.57, 15.37]
1.2 (0.5x starting) 40 mg/day	1	27	Mean Difference (IV, Fixed, 95% CI)	-6.20 [-17.93, 5.53]
1.3 (starting dose) 60 & 80 mg/day	1	39	Mean Difference (IV, Fixed, 95% CI)	-11.50 [-21.60, -1.40]
2 DBP	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 (0.25x starting) 20 mg/day	1	26	Mean Difference (IV, Fixed, 95% CI)	4.2 [-2.33, 10.73]
2.2 (0.5x starting) 40 mg/day	1	27	Mean Difference (IV, Fixed, 95% CI)	0.40 [-6.02, 6.82]
2.3 (starting dose) 60 & 80 mg/day	1	39	Mean Difference (IV, Fixed, 95% CI)	-3.30 [-8.94, 2.34]
3 Pulse pressure	1		Mean Difference (Fixed, 95% CI)	Subtotals only
3.1 (0.25x starting) 20 mg/day	1	26	Mean Difference (Fixed, 95% CI)	5.3 [-5.11, 15.71]
3.2 (0.5x starting) 40 mg/day	1	27	Mean Difference (Fixed, 95% CI)	0.7 [-9.51, 10.91]
3.3 (starting dose) 60 & 80 mg/day	1	39	Mean Difference (Fixed, 95% CI)	2.7 [-7.71, 13.11]

Comparison 7. Pooled partial agonist effects

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SBP	11		Mean Difference (Fixed, 95% CI)	Subtotals only
1.1 0.25x starting dose	1	26	Mean Difference (Fixed, 95% CI)	3.4 [-8.58, 15.38]
1.2 0.5x starting dose	2	82	Mean Difference (Fixed, 95% CI)	-6.12 [-11.36, -0.87]
1.3 starting dose	10	384	Mean Difference (Fixed, 95% CI)	-8.11 [-10.41, -5.81]
1.4 2x starting dose	3	180	Mean Difference (Fixed, 95% CI)	-7.95 [-12.18, -3.72]

1.5 4x starting dose	2	106	Mean Difference (Fixed, 95% CI)	-11.04 [-15.98, -6.10]
2 DBP	11	778	Mean Difference (Fixed, 95% CI)	-3.89 [-4.87, -2.91]
2.1 0.25x starting dose	1	26	Mean Difference (Fixed, 95% CI)	4.2 [-2.33, 10.73]
2.2 0.5x starting dose	2	82	Mean Difference (Fixed, 95% CI)	-0.73 [-4.83, 3.38]
2.3 starting dose	10	384	Mean Difference (Fixed, 95% CI)	-3.81 [-5.08, -2.55]
2.4 2x starting dose	3	180	Mean Difference (Fixed, 95% CI)	-4.41 [-6.53, -2.28]
2.5 4x starting dose	2	106	Mean Difference (Fixed, 95% CI)	-6.71 [-9.72, -3.69]
3 Heart rate	7		Mean Difference (Fixed, 95% CI)	Subtotals only
3.1 0.5x starting dose	1	55	Mean Difference (Fixed, 95% CI)	-2.23 [-7.33, 2.87]
3.2 1x starting dose	7	200	Mean Difference (Fixed, 95% CI)	-5.96 [-7.38, -4.53]
3.3 2x starting dose	2	86	Mean Difference (Fixed, 95% CI)	-2.27 [-4.58, 0.03]
4 Pulse Pressure	11	765	Mean Difference (Fixed, 95% CI)	-3.40 [-4.94, -1.87]
4.1 0.25x starting dose	1	26	Mean Difference (Fixed, 95% CI)	5.3 [-5.11, 15.71]
4.2 0.5x starting dose	2	82	Mean Difference (Fixed, 95% CI)	-2.53 [-9.09, 4.02]
4.3 1x starting dose	10	371	Mean Difference (Fixed, 95% CI)	-3.58 [-5.54, -1.63]
4.4 2x starting dose	3	180	Mean Difference (Fixed, 95% CI)	-3.76 [-7.39, -0.14]
4.5 4x starting dose	2	106	Mean Difference (Fixed, 95% CI)	-3.88 [-8.15, 0.40]
5 WDAE	1	117	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.07, 7.67]
6 Combined starting and twice the starting dose	10		Mean Difference (Fixed, 95% CI)	Subtotals only
6.1 SBP	10	564	Mean Difference (Fixed, 95% CI)	-8.07 [-10.09, -6.05]
6.2 DBP	10	564	Mean Difference (Fixed, 95% CI)	-3.97 [-5.05, -2.88]
6.3 Heart rate	7	286	Mean Difference (Fixed, 95% CI)	-4.94 [-6.15, -3.73]
6.4 Pulse pressure	10	551	Mean Difference (Fixed, 95% CI)	-3.62 [-5.34, -1.90]

Analysis 1.1. Comparison 1 Acebutolol vs Placebo, Outcome 1 SBP.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 1 Acebutolol vs Placebo

Outcome: 1 SBP

Analysis 1.2. Comparison 1 Acebutolol vs Placebo, Outcome 2 DBP.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 1 Acebutolol vs Placebo

Outcome: 2 DBP

Analysis 1.3. Comparison 1 Acebutolol vs Placebo, Outcome 3 Heart rate.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 1 Acebutolol vs Placebo

Outcome: 3 Heart rate

Analysis 1.4. Comparison 1 Acebutolol vs Placebo, Outcome 4 Pulse pressure.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 1 Acebutolol vs Placebo

Outcome: 4 Pulse pressure

Analysis 2.1. Comparison 2 Pindolol vs Placebo, Outcome 1 SBP.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 2 Pindolol vs Placebo

Outcome: 1 SBP

Analysis 2.2. Comparison 2 Pindolol vs Placebo, Outcome 2 DBP.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 2 Pindolol vs Placebo

Outcome: 2 DBP

Analysis 2.3. Comparison 2 Pindolol vs Placebo, Outcome 3 Heart rate.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 2 Pindolol vs Placebo

Outcome: 3 Heart rate

Analysis 2.4. Comparison 2 Pindolol vs Placebo, Outcome 4 Pulse pressure.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 2 Pindolol vs Placebo

Outcome: 4 Pulse pressure

Analysis 3.1. Comparison 3 Celiprolol vs Placebo, Outcome 1 SBP.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 3 Celiprolol vs Placebo

Outcome: 1 SBP

Analysis 3.2. Comparison 3 Celiprolol vs Placebo, Outcome 2 DBP.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 3 Celiprolol vs Placebo

Outcome: 2 DBP

Analysis 3.3. Comparison 3 Celiprolol vs Placebo, Outcome 3 Heart rate.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 3 Celiprolol vs Placebo

Outcome: 3 Heart rate

Analysis 3.4. Comparison 3 Celiprolol vs Placebo, Outcome 4 Pulse pressure.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 3 Celiprolol vs Placebo

Outcome: 4 Pulse pressure

Analysis 3.5. Comparison 3 Celiprolol vs Placebo, Outcome 5 SBP dose comparison.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 3 Celiprolol vs Placebo

Outcome: 5 SBP dose comparison

Analysis 3.6. Comparison 3 Celiprolol vs Placebo, Outcome 6 DBP dose comparison.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 3 Celiprolol vs Placebo

Outcome: 6 DBP dose comparison

Analysis 4.1. Comparison 4 Alprenolol vs Placebo, Outcome 1 SBP.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 4 Alprenolol vs Placebo

Outcome: 1 SBP

Analysis 4.2. Comparison 4 Alprenolol vs Placebo, Outcome 2 DBP.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 4 Alprenolol vs Placebo

Outcome: 2 DBP

Analysis 4.3. Comparison 4 Alprenolol vs Placebo, Outcome 3 Heart rate.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 4 Alprenolol vs Placebo

Outcome: 3 Heart rate

Analysis 4.4. Comparison 4 Alprenolol vs Placebo, Outcome 4 Pulse pressure.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 4 Alprenolol vs Placebo

Outcome: 4 Pulse pressure

Analysis 5.1. Comparison 5 Bopindolol vs Placebo, Outcome 1 SBP.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 5 Bopindolol vs Placebo

Outcome: 1 SBP

Analysis 5.2. Comparison 5 Bopindolol vs Placebo, Outcome 2 DBP.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 5 Bopindolol vs Placebo

Outcome: 2 DBP

Analysis 5.3. Comparison 5 Bopindolol vs Placebo, Outcome 3 Heart rate.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 5 Bopindolol vs Placebo

Outcome: 3 Heart rate

Analysis 5.4. Comparison 5 Bopindolol vs Placebo, Outcome 4 Pulse pressure.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 5 Bopindolol vs Placebo

Outcome: 4 Pulse pressure

Analysis 5.5. Comparison 5 Bopindolol vs Placebo, Outcome 5 WDAE.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 5 Bopindolol vs Placebo

Outcome: 5 WDAE

Analysis 6.1. Comparison 6 Oxprenolol vs Placebo, Outcome 1 SBP.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 6 Oxprenolol vs Placebo

Outcome: 1 SBP

Analysis 6.2. Comparison 6 Oxprenolol vs Placebo, Outcome 2 DBP.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 6 Oxprenolol vs Placebo

Outcome: 2 DBP

Analysis 6.3. Comparison 6 Oxprenolol vs Placebo, Outcome 3 Pulse pressure.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 6 Oxprenolol vs Placebo

Outcome: 3 Pulse pressure

Analysis 7.1. Comparison 7 Pooled partial agonist effects, Outcome 1 SBP.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 7 Pooled partial agonist effects

Outcome: 1 SBP

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Analysis 7.2. Comparison 7 Pooled partial agonist effects, Outcome 2 DBP.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 7 Pooled partial agonist effects

Outcome: 2 DBP

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Analysis 7.3. Comparison 7 Pooled partial agonist effects, Outcome 3 Heart rate.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 7 Pooled partial agonist effects

Outcome: 3 Heart rate

Analysis 7.4. Comparison 7 Pooled partial agonist effects, Outcome 4 Pulse Pressure.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 7 Pooled partial agonist effects

Outcome: 4 Pulse Pressure

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(... Continued)

Analysis 7.5. Comparison 7 Pooled partial agonist effects, Outcome 5 WDAE.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 7 Pooled partial agonist effects

Outcome: 5 WDAE

Analysis 7.6. Comparison 7 Pooled partial agonist effects, Outcome 6 Combined starting and twice the starting dose.

Review: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension

Comparison: 7 Pooled partial agonist effects

Outcome: 6 Combined starting and twice the starting dose

(Continued ...)

(... Continued)

(Continued ...)

(... Continued)

APPENDICES

Appendix I. MEDLINE search strategy

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update
 Search Date: 8 October 2014

- 1 exp adrenergic beta-antagonists/
- 2 (beta adj2 (adrenergic? or antagonist? or block\$ or receptor?)).tw.
- 3 acebutolol.mp.
- 4 exp alprenolol/
- 5 alprenolol.mp.
- 6 amosulalol.mp.
- 7 arotinolol.mp.
- 8 atenolol.mp.
- 9 befunolol.mp.
- 10 betaxolol.mp.
- 11 bevamolol.mp.
- 12 exp bisoprolol/
- 13 bisoprolol.mp.
- 14 bopindolol.mp.
- 15 bucindolol.mp.
- 16 bucumolol.mp.
- 17 bufetolol.mp.
- 18 bufuralol.mp.
- 19 bunitrolol.mp.
- 20 exp bupranolol/

21 bupranolol.mp.
22 butofilolol.mp.
23 carazolol.mp.
24 exp carteolol/
25 carteolol.mp.
26 carvedilol.mp.
27 exp celiprolol/
28 celiprolol.mp.
29 cetamolol.mp.
30 cloranolol.mp.
31 cyanopindolol.mp.
32 deacetylmetipranolol.mp.
33 dihydroalprenolol.mp.
34 dilevalol.mp.
35 epanolol.mp.
36 esmolol.mp.
37 indenolol.mp.
38 iodocyanopindolol.mp.
39 exp labetalol/
40 labetalol.mp.
41 landiolol.mp.
42 exp levobunolol/
43 levobunolol.mp.
44 mepindolol.mp.
45 exp metoprolol/
46 metoprolol.mp.
47 exp metipranolol/
48 metipranolol.mp.
49 moprolol.mp.
50 exp nadolol/
51 nadolol.mp.
52 nadoxolol.mp.
53 nebivolol.mp.
54 nifenalol.mp.
55 nipradilol.mp.
56 oxprenolol.mp.
57 exp penbutolol/
58 penbutolol.mp.
59 exp pindolol/
60 pindolol.mp.
61 exp practolol/
62 practolol.mp.
63 pronethalol.mp.
64 exp propranolol/
65 propranolol.mp.
66 proxodolol.mp.
67 exp sotalol/
68 sotalol.mp.
69 sulfinalol.mp.
70 talinolol.mp.
71 tertatolol.mp.
72 tilisolol.mp.
73 exp timolol/

74 timolol.mp.
 75 toliprolol.mp.
 76 xibenolol.mp.
 77 or/1-76
 78 hypertension/
 79 hypertens\$.tw.
 80 exp blood pressure/
 81 (blood pressure or bloodpressure).mp.
 82 or/78-81
 83 randomized controlled trial.pt.
 84 controlled clinical trial.pt.
 85 randomized.ab.
 86 placebo.ab.
 87 clinical trials as topic/
 88 randomly.ab.
 89 trial.ti.
 90 or/83-89
 91 animals/ not (humans/ and animals/)
 92 90 not 91
 93 77 and 82 and 92

Appendix 2. CENTRAL search strategy

Database: (Wiley) Cochrane Central Register of Controlled Trials <Issue 9 2014>

Search date: 8 October 2014

----- ID Search

#1 MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees
 #2 (acebutolol):ti,ab,kw in Trials
 #3 MeSH descriptor: [Alprenolol] explode all trees
 #4 alprenolol:ti,ab,kw in Trials
 #5 amosulalol:ti,ab,kw in Trials
 #6 arotinolol:ti,ab,kw in Trials
 #7 atenolol:ti,ab,kw in Trials
 #8 befunolol:ti,ab,kw in Trials
 #9 betaxolol:ti,ab,kw in Trials
 #10 bevantolol:ti,ab,kw in Trials
 #11 MeSH descriptor: [Bisoprolol] explode all trees
 #12 bisoprolol:ti,ab,kw in Trials
 #13 bopindolol:ti,ab,kw in Trials
 #14 bucindolol:ti,ab,kw in Trials
 #15 bucumolol:ti,ab,kw in Trials
 #16 bufetolol:ti,ab,kw in Trials
 #17 bufuralol:ti,ab,kw in Trials
 #18 bunitrolol:ti,ab,kw in Trials
 #19 MeSH descriptor: [Bupranolol] explode all trees
 #20 bupranolol:ti,ab,kw in Trials
 #21 butofilolol:ti,ab,kw in Trials
 #22 carazolol:ti,ab,kw in Trials
 #23 MeSH descriptor: [Carteolol] explode all trees
 #24 carteolol:ti,ab,kw in Trials
 #25 carvedilol:ti,ab,kw in Trials

#26 MeSH descriptor: [Celiprolol] explode all trees
 #27 celiprolol:ti,ab,kw in Trials
 #28 cetamolol:ti,ab,kw in Trials
 #29 cloranolol:ti,ab,kw in Trials
 #30 cyanopindolol:ti,ab,kw in Trials
 #31 deacetylmetipranolol:ti,ab,kw in Trials
 #32 dihydroalprenolol:ti,ab,kw in Trials
 #33 dilevalol:ti,ab,kw in Trials
 #34 epanolol:ti,ab,kw in Trials
 #35 esmolol:ti,ab,kw in Trials
 #36 indenolol:ti,ab,kw in Trials
 #37 iodocyanopindolol:ti,ab,kw in Trials
 #38 MeSH descriptor: [Labetalol] explode all trees
 #39 labetalol:ti,ab,kw in Trials
 #40 nebivolol:ti,ab,kw in Trials
 #41 MeSH descriptor: [Levobunolol] explode all trees
 #42 mepindolol:ti,ab,kw in Trials
 #43 mepindolol:ti,ab,kw in Trials
 #44 MeSH descriptor: [Metoprolol] explode all trees
 #45 metoprolol:ti,ab,kw in Trials
 #46 MeSH descriptor: [Metipranolol] explode all trees
 #47 levobunolol:ti,ab,kw in Trials
 #48 nifenalol:ti,ab,kw in Trials
 #49 MeSH descriptor: [Nadolol] explode all trees
 #50 nadolol:ti,ab,kw in Trials
 #51 nadoxolol:ti,ab,kw in Trials
 #52 nebivolol:ti,ab,kw in Trials
 #53 metipranolol:ti,ab,kw in Trials
 #54 nipradilol:ti,ab,kw in Trials
 #55 oxprenolol:ti,ab,kw in Trials
 #56 MeSH descriptor: [Penbutolol] explode all trees
 #57 penbutolol:ti,ab,kw in Trials
 #58 MeSH descriptor: [Pindolol] explode all trees
 #59 pindolol:ti,ab,kw in Trials
 #60 MeSH descriptor: [Practolol] explode all trees
 #61 practolol:ti,ab,kw in Trials
 #62 pronethalol:ti,ab,kw in Trials
 #63 MeSH descriptor: [Propranolol] explode all trees
 #64 propranolol:ti,ab,kw in Trials
 #65 MeSH descriptor: [Sotalol] explode all trees
 #66 sotalol:ti,ab,kw in Trials
 #67 sulfinalol:ti,ab,kw in Trials
 #68 talinolol:ti,ab,kw in Trials
 #69 tertatolol:ti,ab,kw in Trials
 #70 tilisolol:ti,ab,kw in Trials
 #71 MeSH descriptor: [Timolol] explode all trees
 #72 timolol:ti,ab,kw in Trials
 #73 toliprolol:ti,ab,kw in Trials
 #74 xibenolol:ti,ab,kw in Trials
 #75 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #
 39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57
 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 in Trials

#76 MeSH descriptor: [Hypertension] this term only
 #77 hypertens*:ti,ab in Trials
 #78 MeSH descriptor: [Blood Pressure] explode all trees
 #79 "blood pressure":ti,ab,kw in Trials
 #80 #76 or #77 or #78 or #79 in Trials
 #81 #75 and #80 in Trials

Appendix 3. EMBASE search strategy

Database: Embase <1974 to 2014 Week 40>

Search Date: 8 October 2014

1 exp beta adrenergic receptor blocking agent/
 2 (beta adj2 (adrenergic? or antagonist? or block\$ or receptor?)).tw.
 3 acebutolol.mp.
 4 exp alprenolol/
 5 alprenolol.mp.
 6 amosulalol.mp.
 7 arotinolol.mp.
 8 atenolol.mp.
 9 befunolol.mp.
 10 betaxolol.mp.
 11 bevamolol.mp.
 12 exp bisoprolol/
 13 bisoprolol.mp.
 14 bopindolol.mp.
 15 bucindolol.mp.
 16 bucumolol.mp.
 17 bufetolol.mp.
 18 bufuralol.mp.
 19 bunitrolol.mp.
 20 exp bupranolol/
 21 bupranolol.mp.
 22 butofilolol.mp.
 23 carazolol.mp.
 24 exp carteolol/
 25 carteolol.mp.
 26 carvedilol.mp.
 27 exp celiprolol/
 28 celiprolol.mp.
 29 cetamolol.mp.
 30 cloranolol.mp.
 31 cyanopindolol.mp.
 32 deacetylmepitranolol.mp.
 33 dihydroalprenolol.mp.
 34 dilevalol.mp.
 35 epanolol.mp.
 36 esmolol.mp.
 37 indenolol.mp.
 38 iodocyanopindolol.mp.
 39 exp labetalol/
 40 labetalol.mp.

41 landiolol.mp.
 42 exp levobunolol/
 43 levobunolol.mp.
 44 mepindolol.mp.
 45 exp metoprolol/
 46 metoprolol.mp.
 47 exp metipranolol/
 48 metipranolol.mp.
 49 moprolol.mp.
 50 exp nadolol/
 51 nadolol.mp.
 52 nadoxolol.mp.
 53 nebivolol.mp.
 54 nifenalol.mp.
 55 nipradilol.mp.
 56 oxprenolol.mp.
 57 exp penbutolol/
 58 penbutolol.mp.
 59 exp pindolol/
 60 pindolol.mp.
 61 exp practolol/
 62 practolol.mp.
 63 pronethalol.mp.
 64 exp propranolol/
 65 propranolol.mp.
 66 proxodolol.mp.
 67 exp sotalol/
 68 sotalol.mp.
 69 sulfinalol.mp.
 70 talinolol.mp.
 71 tertatolol.mp.
 72 tilisolol.mp.
 73 exp timolol/
 74 timolol.mp.
 75 toliprolol.mp.
 76 xibenolol.mp.
 77 or/1-76
 78 exp hypertension/
 79 hypertens\$.tw.
 80 (blood pressure or bloodpressure).mp.
 81 or/78-80
 82 randomized controlled trial/
 83 crossover procedure/
 84 double-blind procedure/
 85 (randomized or randomly).ab.
 86 (crossover\$ or cross-over\$).tw.
 87 placebo\$.ab.
 88 (doubl\$ adj blind\$).tw.
 89 or/82-88
 90 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
 91 89 not 90
 92 77 and 81 and 91

Appendix 4. ClinicalTrials.gov

Database: ClinicalTrials.gov (via Cochrane Register of Studies)

Search Date: 9 October 2014

Study type: Interventional Studies

Conditions: hypertension

Interventions: (beta blocker) or (adrenergic beta-antagonist)

Outcome Measures: blood pressure

Search terms: randomized

Appendix 5. Hypertension Group Specialised Register search strategy

Database: Hypertension Group Specialised Register

Search Date: 14 October 2014

1 adrenergic beta-antagon*

2 beta blocker*

3 adrenergic block*

4 #1 OR #2 OR #3

5 ((RCT OR Review OR Meta-Analysis):DE) AND (INREGISTER)

6 #4 AND #5

HISTORY

Date	Event	Description
18 June 2010	Amended	Amended protocol: added second author; added double blind and crossover studies in inclusion criteria. Updated background, search methods and references

CONTRIBUTIONS OF AUTHORS

James Wright formulated the idea for the review and developed the basis for the protocol.

Gavin Wong took the lead role in searching, identifying and assessing studies, in data extraction and analyses, and in writing up the review.

Heidi Boyda aided in the data extraction process and approved the final draft of the manuscript.

DECLARATIONS OF INTEREST

James Wright: nothing to declare.

Gavin Wong: nothing to declare.

Heidi Boyda: nothing to declare.

SOURCES OF SUPPORT

Internal sources

- University of British Columbia, Department of Anesthesiology, Pharmacology & Therapeutics, Canada.

External sources

- Canadian Institutes of Health Research, Canada.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic beta-1 Receptor Antagonists [*therapeutic use]; Antihypertensive Agents [*therapeutic use]; Blood Pressure [*drug effects]; Dose-Response Relationship, Drug; Essential Hypertension; Heart Rate [drug effects]; Hypertension [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans