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[Intervention Review]

Blood pressure lowering efficacy of dual alpha and beta blockers for primary hypertension

Gavin WK Wong¹, Alexandra Laugerotte¹, James M Wright¹¹Department of Anesthesiology, Pharmacology and Therapeutics, University of British Columbia, Vancouver, Canada**Contact:** Gavin WK Wong, Department of Anesthesiology, Pharmacology and Therapeutics, University of British Columbia, 2176 Health Sciences Mall, Vancouver, BC, V6T 1Z3, Canada. gavin.wong@ti.ubc.ca.**Editorial group:** Cochrane Hypertension Group.**Publication status and date:** New, published in Issue 8, 2015.**Citation:** Wong GWK, Laugerotte A, Wright JM. Blood pressure lowering efficacy of dual alpha and beta blockers for primary hypertension. *Cochrane Database of Systematic Reviews* 2015, Issue 8. Art. No.: CD007449. DOI: [10.1002/14651858.CD007449.pub2](https://doi.org/10.1002/14651858.CD007449.pub2).

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ABSTRACT

Background

Drugs with combined alpha and beta blocking activity are commonly prescribed to treat hypertension. However, the blood pressure (BP) lowering efficacy of this class of beta blockers has not been systematically reviewed and quantified.

Objectives

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

Search methods

We searched the Cochrane Hypertension Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, 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 blind placebo controlled parallel or cross-over trials. Studies contained a beta blocker monotherapy arm with a fixed dose. Patients enrolled in the studies had primary hypertension at baseline. Duration of the studies was from three to 12 weeks. Drugs in this class of beta blockers are carvedilol, dilevalol and labetalol.

Data collection and analysis

Two review authors (GW and AL) confirmed the inclusion of studies and extracted the data independently. RevMan 5.3 was used to synthesize data.

Main results

We included eight studies examining the blood pressure lowering efficacy of carvedilol and labetalol in 1493 hypertensive patients. Five of the included studies were parallel design; three were cross-over design. The two largest included studies were unpublished carvedilol studies. The estimates of BP lowering effect (systolic BP/diastolic BP millimeters of mercury; SPB/DBP mm Hg) were -4 mm Hg (95% confidence intervals (CI) -6 to -2)/-3 mm Hg (95% CI -4 to -2) for carvedilol (>1000 subjects) and -10 mm Hg (95% CI -14 to -7)/-7 mm Hg (95% CI -9 to -5) for labetalol (110 subjects). The effect of labetalol is likely to be exaggerated due to high risk of bias. Carvedilol, within the recommended dose range, did not show a significant dose response effect for SBP or DBP. Carvedilol had little or no effect on pulse pressure (-1 mm Hg) and did not change BP variability. Overall, once and twice the starting dose of carvedilol and labetalol lowered BP by -6 mm Hg (95% CI -7 to -4) /-4 mm Hg (95% CI -4 to -3) (low quality evidence) and lowered heart rate by five beats per minute (95% CI

-6 to -4) (low quality evidence). Five studies (N = 1412) reported withdrawal due to adverse effects; the risk ratio was 0.88 (95% CI 0.54 to 1.42) (moderate quality evidence).

Authors' conclusions

This review provides low quality evidence that in patients with mild to moderate hypertension, dual receptor blockers lowered trough BP by an average of -6/-4 mm Hg and reduced heart rate by five beats per minute. Due to the larger sample size from the two unpublished studies, carvedilol provided a better estimate of BP lowering effect than labetalol. The BP lowering estimate from combining carvedilol once and twice the starting doses is -4/-3 mm Hg. Doses higher than the recommended starting dose did not provide additional BP reduction. Higher doses of dual receptor blockers caused more bradycardia than lower doses. Based on indirect comparison with other classes of drugs, the blood pressure lowering effect of dual alpha- and beta-receptor blockers is less than non-selective, beta1 selective and partial agonist beta blockers, as well as thiazides and drugs inhibiting the renin angiotensin system. Dual blockers also had little or no effect on reducing pulse pressure, which is similar to the other beta-blocker classes, but less than the average reduction of pulse pressure seen with thiazides and drugs inhibiting the renin angiotensin system. Patients taking dual receptor blockers were not more likely to withdraw from the study compared to patients taking placebo.

PLAIN LANGUAGE SUMMARY

Alpha and beta dual receptor blockers for treatment of high blood pressure

Background

Alpha and beta dual receptor blockers are a subclass of beta blockers which are commonly used to treat high blood pressure (BP). Drugs in this class include carvedilol (Coreg), labetalol (Trandate) and dilevalol (Unicard). We searched for and found all the relevant studies to examine how well this class of drugs lowered blood pressure.

Study characteristics

We found eight clinical studies in October 2014, that examined the blood pressure lowering effect of carvedilol and labetalol in 1493 participants with high blood pressure. These people were randomly assigned to receive either a fixed dose of dual receptor blockers or a placebo for 3 to 12 weeks.

Key results

On average, dual receptor blockers lowered systolic BP by six points, diastolic BP by four points and heart rate by five beats per minute in patients with mild to moderate high blood pressure. There were more data on the effects of carvedilol. On average, carvedilol lowered systolic BP by four points and diastolic BP by three points. Higher doses of dual receptor blockers caused more slowing of heart rate but not more lowering of BP. The BP lowering effect of dual receptor blockers was less than other classes of BP lowering drugs. Patients taking dual receptor blockers were not more likely to withdraw from the study compared to patients taking placebo.

Quality of the evidence

The quality of the evidence was judged to be low due to various types of bias that could exaggerate the effect. A low quality of evidence means future research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Dual receptor blockers compared with placebo for primary hypertension

Patient or population: Adults with primary hypertension

Intervention: Alpha and beta dual receptor blockers

Comparison: Placebo

Outcomes	Mean estimates of combining once and twice starting dose (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
Systolic blood pressure	-5.59 (95% CI -7.47 to -3.70) ^{1,2,3}	1007 (8)	Low ^{4,5}
Diastolic blood pressure	-3.88 (95% CI -4.95 to -2.82) ^{1,2,3}	1007 (8)	Low ^{4,5}
Heart rate	-4.62 (95% CI -5.71 to -3.54) ^{1,2}	977 (7)	Low ^{4,5}
Pulse pressure	-1.89 (95% CI -3.58 to -0.20) ^{1,2}	1007 (8)	Very low ^{4,5,6}
WDAE	0.88 (95% CI 0.54 to 1.42)	1412 (5)	Moderate ⁷

SBP: systolic blood pressure; DBP: diastolic blood pressure; WDAE: withdrawal due to adverse effects; 95%CI: 95% confident interval

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. The recommended starting and 2x starting contained most of the data in dual blockers analysis. Combining them provided estimates that represent the overall subclass effect.
2. Most of the measurements were made at trough hours.
3. Weighted mean baseline DBP was 101 mmHg.
4. Quality of evidence was downgraded one level due to high risk of detection bias caused by breaking of blinding.
5. Quality of evidence was downgraded one level due to high risk of publication bias in labetalol studies.
6. Quality of evidence was downgraded one level due to indirectness, none of the studies included reported pulse pressure. Pulse pressure was calculated by subtracting DBP from SBP.
7. Quality of evidence was downgraded one level due to imprecision.

BACKGROUND

This review is part of a series of four Cochrane reviews, which also includes reviews studying the blood pressure lowering efficacy of non-selective beta blockers (Wong 2014a), beta-1 selective beta blockers (Wong 2008) and partial agonist beta blockers (Wong 2014b).

Description of the condition

Elevated blood pressure is a 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 in patients with moderate to severe elevations of blood pressure (Musini 2009; Wright 2009). There are a number of classes of antihypertensive drugs used to treat elevated blood pressure. Beta adrenergic receptor blockers (beta blockers) are one class of these drugs.

Description of the intervention

Beta blockers were originally marketed and used to treat angina. During their use in patients with angina, it was discovered that they also lowered 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.

Six systematic reviews are relevant to this proposed review. Wright 2000 assessed the mortality and morbidity associated with different types of beta blockers. The authors found that patients treated with non-selective beta blockers post-myocardial infarction had statistically significant reduction in total mortality 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 (Wisonge 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 this only relates to beta1-selective beta blockers, as atenolol, a beta1-selective beta blocker, was the beta blocker used in 75% of the studies.

Wright 2009 examined the mortality and morbidity outcomes of different classes of first-line antihypertensive drugs in people with hypertension. This review found that beta blockers significantly reduced stroke and cardiovascular events but not all cause mortality and congestive heart disease (CHD). The clinical outcome results of beta blockers were inferior to low-dose thiazides, ACE inhibitors and calcium channel blockers.

Three systematic reviews have assessed the effects of beta blockers on blood pressure. A Cochrane review of beta blockers for hypertension during pregnancy showed that oral beta blockers decreased the incidence of severe hypertension and the need for additional antihypertensive therapy (Magee 2003). A systematic review of the dose-response blood pressure lowering effect of beta blockers and other antihypertensive drugs was limited by the fact that it did not differentiate between the different classes of beta blockers (Law 2005). Finally, a Cochrane review of the blood pressure lowering efficacy of beta blockers as a second-line treatment did not have enough studies to be able to differentiate between the different classes of beta blockers (Chen 2010a).

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 in humans is not known. Many hypothetical mechanisms have been proposed, which include: decreasing cardiac output, reducing renin production or modulating the sympathetic nervous system. It is likely that a combination of these mechanisms causes the blood pressure lowering effect.

There are two major types of adrenergic receptors: alpha and beta. Alpha adrenergic receptors are divided into two subtypes, alpha1 and alpha2. Alpha1 receptors participate in the regulation of cardiac contractility, heart rate, hepatic glucose release and vasoconstriction of the aorta, coronary artery and large resistance blood vessels. Alpha2 receptors are the dominant receptors that participate in vasoconstriction of pro-capillary arterioles and central nervous system (CNS) negative feedback to inhibit the production of norepinephrine. Activation of alpha adrenergic receptors through reflex sympathetic activation would cause vasoconstriction and therefore raise blood pressure. This effect could counter the blood pressure lowering effect of beta adrenergic antagonism. Beta receptors have three subtypes. Beta1 and beta2 are the two subtypes that participate in cardiovascular regulation. The beta1 receptor is the dominant beta receptor that mediates the catecholamine effect in the heart. Activation of beta1 receptors increases heart rate and therefore cardiac output. Beta2 receptors primarily regulate peripheral beta-adrenergic responses such as vasodilation, bronchodilation and the release of renin and lipolysis in various tissues (Goodman 2011).

Dual alpha and beta-blocking drugs were designed to competitively inhibit both alpha and beta receptors. Currently, there are no known selective antagonists for beta3 receptors. Dual alpha and beta blockers have both alpha and beta-blocking properties but no partial agonist activity. These drugs may be non-selective or beta1 selective on beta receptors as well as selectively blocking alpha1 or alpha2 receptors. Carvedilol (Coreg), dilevalol and labetalol (Trandate) are the drugs that fit into this pharmacological class. Both carvedilol and labetalol are non-selective beta blockers and have higher affinity to alpha1 receptors than alpha2 receptors (Goodman 2011).

Why it is important to do this review

Since it is possible that beta blockers with different mechanisms of action have different effects on the reduction of morbidity and mortality, it is crucial to determine whether they have different abilities to lower blood pressure. No published review has quantified the blood pressure lowering effect of beta blockers according to their subclass of beta-blocking activity. This review could provide important information towards understanding the mechanism by which beta blockers lower blood pressure.

Furthermore, since physicians use blood pressure lowering drugs on a daily basis to manage patients with high blood pressure, it is important to know accurately the magnitude of blood pressure lowering effect of individual beta blockers and separate subclasses.

The information found in this review would be useful for clinicians, scientists designing future drug trials and authors of other systematic reviews.

OBJECTIVES

Primary objective

To quantify the dose-related effects of various doses and types of dual alpha and beta adrenergic receptor blockers on systolic and diastolic blood pressure versus placebo in patients with primary hypertension.

Secondary objectives

1. To determine the effects of dual alpha and beta adrenergic receptor blockers on variability of blood pressure.
2. To determine the effects of dual alpha and beta adrenergic receptor blockers on pulse pressure.
3. To quantify the dose-related effects of dual alpha and beta adrenergic receptor blockers on heart rate.
4. To quantify the effects of dual alpha and beta adrenergic receptor blockers in different doses on withdrawals due to adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

Study design met 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 at least three weeks;
- blood pressure measurements at baseline (following washout) and at one or more time points between 3 and 12 weeks after starting treatment.

Types of participants

Participants had a baseline blood pressure of at least 140 mm Hg systolic, a diastolic blood pressure of at least 90 mm Hg, or both, measured in a standard way. Patients did not have creatinine levels greater than 1.5 times the normal level. Participants were not restricted by age, gender, baseline risk or other co-morbid conditions.

Types of interventions

Monotherapy with any dual alpha and beta adrenergic receptor blocker, including carvedilol, dilevalol or labetalol.

Studies 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), peak (1 to 12 hours after the dose) or both systolic and diastolic blood pressure compared to placebo. If blood pressure measurements were available at more than one time within the acceptable

window, the weighted means of blood pressures taken in the 3 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 effects compared to placebo.

Search methods for identification of studies

We searched the Database of Abstracts of Reviews of Effects (DARE; October 2014) for related reviews. We used previously published meta-analyses on dose-response of beta adrenergic receptor blockers to help identify references to studies.

We searched the Cochrane Hypertension Group Specialised Register (October 2014), the Cochrane Central Register of Controlled Trials (CENTRAL; 2014, Issue 9), MEDLINE (1946 to October 2014), EMBASE (1974 to October 2014) and ClinicalTrials.gov (all years to October 2014) for randomized controlled trials. We applied no language restrictions. 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](#)).

We searched all the databases to identify potentially relevant citations. The initial screening of these abstracts excluded articles whose titles and abstracts indicated they were clearly irrelevant. The full text of remaining articles were retrieved (and translated into English where required). We searched the bibliographies of pertinent articles, reviews and texts for additional citations.

Data collection and analysis

Selection of studies

We imported the references and abstracts identified by our search into Reference Manager 11 software. We selected studies based on the criteria listed above. Two independent review authors assessed the eligibility of the studies using a study selection form. A third reviewer resolved discrepancies.

Data extraction and management

Two review authors independently extracted data using a standard form and then cross-checked them. A second person confirmed all numeric calculations and graphic interpolations.

Assessment of risk of bias in included studies

We assessed the risk of bias with the standard Cochrane 'Risk of bias' tool. The domains assessed included allocation sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, completeness of participant

follow-up, handling of incomplete outcome data and protection against selective outcome reporting.

Measures of treatment effect

The position of the patient during blood pressure measurement might affect the blood pressure reading or true lowering effect. However, in order not to lose valuable data, data reported from any single positions were used, regardless of the position. When blood pressure measurement data were available from more than one position, sitting blood pressure was the first preference. If both standing and supine were available, standing blood pressure was used. Effect measures were reported as the mean difference (MD) in BP, heart rate and pulse pressure between the treatment and placebo groups with 95% confidence interval (CI). Risk ratio (RR) was reported for withdrawal due to adverse effects.

Dealing with missing data

In the case of missing information in the included studies, we contacted the investigators (using email, letter, fax or a combination) to obtain the missing information.

In the case of missing standard deviations (SD) of the change in blood pressure, we imputed the standard deviation, based on the information in the same study or from other studies 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 (unless this measure was used for entry criteria);
5. mean standard deviation of change in blood pressure from other studies using the same drug.

Assessment of heterogeneity

We test for heterogeneity of treatment effect between the studies by using a standard χ^2 statistic for heterogeneity. We used the fixed-effect model to obtain summary statistics of pooled studies, unless significant between-study heterogeneity was present, in which case we used the random-effects model.

Data synthesis

We used the Cochrane Review Manager software, RevMan 5.3 for data syntheses and analyses.

We combined data for changes in blood pressure and heart rate using a weighted mean difference method (WMD). We analyzed drop-outs due to side effects by using relative risk. When we found statistically significant relative risk, we calculated risk difference, and number needed to harm.

When we used the generic inverse variance method to incorporate cross-over studies into meta-analysis, we used the formula listed

in the *Cochrane Handbook for Systematic Reviews of Interventions*, section 16.4.6.1 (Higgins 2011) to calculate the standard deviation of the difference between treatment and placebo. The standard error and sample sizes shown in the data analyses tables were unadjusted for subgroup comparisons in order to minimize the loss of statistical power for the estimates. To avoid double counting of patients when comparing multiple subgroups or combining two subgroups for overall estimates, we adjusted the standard error or the sample size in analyses for studies containing multiple dosage subgroups.

Subgroup analysis and investigation of heterogeneity

If possible, subgroup analyses included:

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

Sensitivity analysis

The robustness of the results were tested using several sensitivity analyses, including:

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

RESULTS

Description of studies

Results of the search

In order to save time and effort, our trial search coordinator developed a comprehensive search strategy so that all four subclasses of beta blockers were searched simultaneously (Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5) and three additional beta blocker reviews (Wong 2008; Wong 2014a; Wong 2014b) used the same study inclusion criteria. Citations were 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; subsequent searches were performed up to October 2014. We identified a total of 22,195 citations, 8353 of which were confirmed to be duplicates. The review authors then screened 13,842 titles and abstracts, 13,229 citations of which were excluded. Based on titles and abstracts, they judged that 613 potentially met the inclusion criteria; these were retrieved for detailed review. Four hundred and ninety-seven full-text articles did not meet our inclusion criteria and were excluded. One hundred and fifteen studies met our inclusion criteria. Twelve studies, among the 115 studies, studied dual receptor blockers. Four studies were excluded with reasons listed in the [Characteristics of excluded studies](#) table. Eight studies were included in this 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 eight RCTs, that examined the blood pressure lowering efficacy of dual receptor blockers in 1493 hypertensive patients for 3 to 12 weeks. Five of the eight included studies were parallel studies; the other three were cross-over studies. Four RCTs studied 12.5 mg/day to 50 mg/day doses of carvedilol in 1381 patients; the other four RCTs studied 300 mg/day to 800 mg/day doses of labetalol in 112 patients. Weighted mean baseline DBP was 101 millimetres of mercury (mm Hg) in carvedilol studies and 105 mm Hg in labetalol studies. Baseline SBP was not given in most included studies.

Excluded studies

Four studies that met the inclusion criteria were excluded after detailed reading. The reasons for exclusion were lack of useful data for outcomes listed in the review and misleading information on methods. Please refer to the [Characteristics of excluded studies](#) table for the reasons of exclusion.

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 of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias): Hemodynamic data	Incomplete outcome data (attrition bias): Clinical outcomes	Selective reporting (reporting bias)
Carvedilol GSK B100	?	?	+	-	+	+	+
Carvedilol GSK B101	?	?	+	-	+	+	+
Frick 1976	?	?	+	+	?	-	-
Kane 1976	+	+	+	?	+	+	+
Lechi 1982	+	+	+	-	-	-	+
McPhillips 1988	?	?	+	-	+	+	-
Rouffy 1986	?	?	+	-	-	-	+
Weber 2006	?	?	+	-	+	+	+

Allocation

Kane 1976 and Lechi 1982 described the details of methods of randomization and allocation concealment. The other six included studies did not report any information on this matter, therefore, it was difficult to assess the risk of bias in this category. The baseline characteristics of parallel groups were similar, thus we did not find any evidence that suggested randomization was not properly done. It was impossible to assess the integrity of randomization in cross-over studies without additional information. Five out of 8 of the included studies in this review were parallel studies therefore the risk of selection bias was low in this review. Even though we did not find any evidence to suspect any bias in randomization and allocation concealment, more precise reporting would allow us to better assess the risk of bias and quality of the evidence.

Blinding

Beta blockers generally present a high risk of detection bias as they lower heart rate. It was likely possible for assessors to detect the treatment group based on the change in heart rate. This risk could be mitigated by using an automated BP machine. However, none of the studies in this review reported using automated BP machines. Therefore, the risk for detection and performance bias was high in this review (Jadad 1996).

Incomplete outcome data

All but one included study, Frick 1976, reported the information on dropouts. The dropout rate was low in the included studies. Therefore the risk of attrition bias was low in this review.

Selective reporting

McPhillips 1988 did not report the data for heart rate according to intervention groups and Frick 1976 did not report withdrawal due to adverse effects (WDAE). Other than that, blood pressure and heart rate were reported in all studies. In addition, five of the eight studies reported useful WDAE. We judged that the risk of selective reporting bias was low in this review.

Publication bias

It is possible that large pivotal studies that would have been required to support the application for a FDA approval for labetalol were not published. As a result, the magnitude of the blood pressure lowering effect was likely over-estimated for labetalol. It is important that both positive and negative data are made available to provide the best estimate of the true effect.

Effects of interventions

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

Carvedilol

Carvedilol is indicated for the treatment of hypertension, left ventricular dysfunction following MI and heart failure in the U.S. (FDA). It is indicated only for heart failure in Canada (eCPS). However, it can be used off label for hypertension. The recommended doses for hypertension in the U.S. are 6.25 mg twice daily to 25 mg twice daily for the immediate release form and 20 to 80 mg daily for the controlled release form.

We included four studies that examined the blood pressure lowering efficacy of 6.25 to 50 mg/day carvedilol in 1381 mild to

moderate hypertensive patients (Carvedilol GSK B100; Carvedilol GSK B101; McPhillips 1988; Weber 2006). Carvedilol GSK B100 and Carvedilol GSK B101 were two unpublished RCTs obtained from the manufacturer's web-site. The unpublished data contributed 72% of the data (1000 of 1381 subjects). Patients enrolled in these studies were on average 52 to 56 years old, with no co-morbidities that could affect their blood pressure. The weighted mean baseline DBP of the four included studies was 100.9 mm Hg. Three of the four studies measured blood pressure at trough hours (Carvedilol GSK B100; Carvedilol GSK B101; Weber 2006).

Carvedilol 6.25 mg/day did not significantly lower SBP or DBP compared to placebo (SBP = -1 mmHg [-5, 3]; DBP = -1 mmHg [-3, 2]; Analysis 1.1 & Analysis 1.2). Starting from 12.5 mg/day (the recommended starting dose), carvedilol significantly lowered SBP and DBP compared to placebo (Analysis 1.1 & Analysis 1.2). Heterogeneity was not significant in any of the subgroups ($I^2=0\%$). All 4 studies had multiple dose subgroups, allowing direct comparison between doses. Tests for subgroup differences by direct comparison were not significant for SBP and DBP within the product monograph range of recommended doses. (12.5 mg/day, 25 mg/day and 50 mg/day). The 1x and 2x starting dose (12.5 mg/day and 25 mg/day) subgroups contained the largest patient sample in carvedilol. The estimate for combining the average trough BP lowering effect combining the 1x and 2x starting dose (12.5 mg/day and 25 mg/day) carvedilol was -4/-3 mmHg.

Carvedilol 6.25 mg/day did not significantly lower heart rate compared to placebo (-1 BPM [-4, 1]; Analysis 1.3). Tests for subgroup differences between carvedilol 12.5 mg/day and higher doses were significant for heart rate ($P < 0.0005$; Analysis 1.3). Carvedilol did not significantly change pulse pressure compared to placebo in any of the dose subgroups (Analysis 1.4).

Blood pressure variability was assessed by comparing the end treatment SD of carvedilol and placebo groups with a t-test. Twelve SDs from carvedilol subgroups and four SDs from placebo subgroups were included. Carvedilol did not significantly change blood pressure variability in SBP ($P = 0.37$) or DBP ($P = 0.65$). The weighted mean SD for carvedilol group (SBP/DBP) was 15.9/9.0 and for placebo group was 16.4/9.2.

Labetalol

Labetalol is indicated for the treatment of hypertension in both Canada and the U.S. (eCPS; FDA). The recommended doses for hypertension in U.S. and Canada are 100 mg twice a day to 400 mg twice a day.

Four studies examined the BP lowering efficacy of 400 to 800 mg/day labetalol in 112 hypertensive patients were included in the analysis (Frick 1976; Kane 1976; Lechi 1982; Rouffy 1986). The baseline characteristics of patients were not well described in the articles. The mean baseline BP of patients enrolled in the studies was 165/105 mm Hg. Sixty per cent of the patients were middle age men with no co-morbidities.

We did not find any data for the recommended starting dose (200 mg/day) of labetalol. Both labetalol 400 and 800 mg/day subgroups significantly lowered SBP and DBP (Analysis 2.1; Analysis 2.2). Tests for subgroup differences were significant by direct comparison for SBP ($p = 0.09$) and DBP ($p = 0.0006$). Heterogeneity was not significant in any of the subgroups (both $I^2=0\%$). Both 400 and 800

mg/day labetalol significantly lowered heart rate (400 mg/day :-7 BPM [-9, -5]; 800 mg/day -8 [-10, -5]; [Analysis 2.3](#)). The effect on heart rate was not significantly different between 400 and 800 mg/day labetalol ($p=0.6$).

Labetalol 400 mg/day significantly reduced pulse pressure (-4 mmHg [-7, -0], $p=0.02$; [Analysis 2.4](#)), but 800 mg/day subgroup did not significantly change pulse pressure (-5 [-10, 0], $p=0.07$; [Analysis 2.4](#)).

Pooled hemodynamic effects of dual blockers

Our analyses showed that the BP lowering effect of carvedilol was much smaller than labetalol. If the difference in effect size was true, it would not be appropriate to pool the data. However, the difference of effect size might be the result of small sample size or bias. The possible reasons for the differences between the drugs are explained in the discussion. Since only carvedilol provided data for the recommended starting dose (12.5 mg/day), the pooled effect size at the recommended starting doses was the same as carvedilol. Dual blocker lowered BP (SBP/DBP) by -6 mmHg [-8, -4]/-4 mmHg [-5, -3] at twice the recommended starting dose (25 mg/day carvedilol and 400 mg/day labetalol). The BP lowering effect was -9 mmHg [-12, -7]/-7 mmHg [-8, -5] at four times the recommended starting dose (50 mg/day carvedilol and 800 mg/day labetalol). Please refer to [Analysis 3.1](#); [Analysis 3.2](#); [Analysis 3.3](#); [Analysis 3.4](#); [Analysis 3.5](#) for the pooled effect of dual alpha and beta blockers.

[Summary of findings for the main comparison](#) also summarizes the results for combining the starting dose and twice the starting dose ([Analysis 4.1](#); [Analysis 4.2](#); [Analysis 4.3](#); [Analysis 4.4](#)).

Withdrawal due to adverse effects (WDAE)

We pooled the WDAE data of carvedilol and labetalol together in order to include all valuable data. Five studies provided data for WDAE in 1412 patients ([Carvedilol GSK B100](#); [Carvedilol GSK B101](#); [McPhillips 1988](#); [Rouffy 1986](#); [Weber 2006](#)). Four of the studies used carvedilol as the active treatment ([Carvedilol GSK B100](#); [Carvedilol GSK B101](#); [McPhillips 1988](#); [Weber 2006](#)). There was no significant difference in relative risk (RR) of WDAE between dual blocker treatment and placebo (RR 0.88; 95% CI 0.54 to 1.42; $P = 0.6$).

Subgroup and sensitivity analyses

With the exception of baseline BP, the baseline characteristics of patients were similar in all studies. None of the studies reported data separated by subgroups. Therefore, the subgroup analyses for sex, co-morbid conditions, race, age or severity of disease was not possible.

Difference between published and unpublished data

We performed a sensitivity analysis in order to examine the differences between estimated mean effect size of published and unpublished studies. The estimated means (SBP/DBP) for the 2x starting dose subgroup (25 mg/day carvedilol and 400 mg/day labetalol) from the published data were -3/-4 mm Hg as compared to -5/-2 mm Hg from the unpublished data. The estimate of SBP/DBP in 4x starting dose (50 mg/day carvedilol and 800 mg/day labetalol) subgroup from published data was -8/-7 mm Hg as compared to -5/-4 mm Hg from the unpublished data. For the 50 mg/day carvedilol and 800 mg/day labetalol, the published estimate exceeded the unpublished estimate by -3/-3 mm Hg.

DISCUSSION

Summary of main results

Carvedilol

Carvedilol 12.5 mg/day and higher doses significantly lowered blood pressure (BP). This finding coincided with the product monograph recommendation. However, the current evidence was inconclusive whether there was a dose response effect. The BP lowering point estimates were higher for higher doses, but the tests for subgroup differences were not significant. The large number of subjects in carvedilol studies, particularly the data coming from the unpublished studies, provided good estimates of the blood pressure lowering effect of carvedilol. The average trough BP lowering effect of once (12.5 mg/day carvedilol) and twice (25 mg/day carvedilol) the recommended starting dose was only -4/-3 mm Hg. This suggested that carvedilol was relatively ineffective at lowering BP compared to other classes of antihypertensive drugs or other beta blockers.

Differences in BP lowering effect between carvedilol and labetalol

The number of patients included in studies for labetalol was much smaller than for carvedilol. In addition, we did not find any data for 200 mg/day labetalol, which was the recommended starting dose. This suggested that some studies of the BP lowering effect of labetalol have been conducted but have never been published. From the studies available, labetalol appeared to significantly lower BP to a greater extent than carvedilol. The average peak BP lowering effect of labetalol at twice (400 mg/day labetalol) the recommended starting dose was -10 [-14, -7]/-7 [-9, -5].

The pharmacology of both dual blockers was examined in order to explore the possible explanation for the differences. In basic pharmacology studies, carvedilol and labetalol showed similar properties in pharmacokinetic parameters such as time to maximum serum concentration, elimination half life and receptor affinity (eCPS; FDA; [Goodman 2011](#); [McTavish 1993](#)). This suggests that the difference in BP lowering effect that we observed was unlikely to be the result of differences in pharmacological properties.

Next, we examined the differences in baseline BP. The mean baseline blood pressure of labetalol studies (105 mm Hg) was higher than in the carvedilol studies (101 mm Hg). Because of this, the absolute blood pressure lowering effect could be bigger for labetalol. However, if the BP lowering was expressed as the DBP percent change from baseline, it was still larger for labetalol (-6%) as compared to carvedilol (-4%). This suggested that differences in baseline BP could only partly explain the differences in effect size.

Three of the four carvedilol studies stated that the blood pressure was measured at trough hours (from 13 to 24 hours after last dose). None of the labetalol studies specified whether blood pressure was measured at peak or trough hours. However, since labetalol was taken two to three times a day, the blood pressure must have been measured at peak hours (from 1 to 12 hours after the dose) in these studies. Measurements during the peak effect time could result in greater blood pressure lowering effect. Therefore, the difference in time of measurements could also contribute to the difference in effect size.

The paucity of large studies assessing the BP lowering effect of labetalol indicated that the pivotal studies that would have been required to achieve a license in various developed countries have not been published and the evidence supporting the use of labetalol for hypertension was weak. Our search for unpublished data for labetalol did not yield any additional studies. The pharmacological properties, basic study design and study population were similar in carvedilol and labetalol studies. Compared to the smaller effect size for carvedilol, the labetalol estimates could be exaggerated due to lack of large pivotal studies. If the difference in baseline BP and time of measurements were taken into account, it is possible that the effect sizes of the two drugs are actually not different. In addition, labetalol needs to be taken two to three times a day compared to the carvedilol controlled-release tablet, which is taken once daily for hypertension. Physicians and patients making decisions to use dual blockers should be made aware of the small BP lowering effect of this class of drugs.

Differences in published and unpublished data

From the sensitivity analysis with carvedilol, we found that published studies could overestimate the BP lowering effect by as much as -3 mm Hg systolic and -3 mm Hg diastolic compared to unpublished studies. This was one of the first examples in which the effect of publication bias could be quantified. It showed the amount of over-estimation caused by a deliberate decision to publish studies that showed greater effect, while not publishing studies that showed less effect. This provides good support for the extra effort it takes to look for unpublished data. However, despite our efforts to search, many studies remained completely hidden. Cochrane has been advocating for the publication of all data, positive and negative, for many years. In recent years, pressure from Cochrane and the European regulatory agency has resulted in the release of some unpublished data from the industry ([NY Times 2013](#)).

In addition, the public are becoming more aware of the impact that publication bias may have on medical decision-making. This is a positive change. It is likely that the unpublished data we found on the GlaxoSmithKline (GSK) web site are the result of the efforts by many Cochrane researchers pushing the company to release all RCT data.

Overall completeness and applicability of evidence

This review provides the most current evidence for the BP lowering efficacy of dual blockers. The studies included in this review fit our objectives in terms of population, goal of the studies and outcomes measured. Our search strategy was comprehensive and thorough. In addition to published data, our extensive search also led us to obtain unpublished data. Therefore, we are confident that this review represents the best evidence available for BP lowering efficacy of these drugs.

Quality of the evidence

[Summary of findings for the main comparison](#) summarizes the effect size of the starting dose and twice the starting dose and provides a judgment of the quality of evidence in this review. This review included eight studies examining two dual blockers in 1493 hypertensive patients. The sample size was sufficient to allow a robust conclusion with regard to carvedilol, primarily because we were able to obtain data on two large unpublished RCTs. However,

like all systematic reviews, we were limited by the data that were available to us.

The data were insufficient for labetalol and we found no RCTs for dilevalol. As discussed above, data from large pivotal studies were missing in the labetalol analyses. As a result, the magnitude of the blood pressure lowering effect was likely over-estimated for labetalol. For this reason, the risk of publication bias for labetalol is high. The risk of publication bias for carvedilol is much lower because of the two unpublished studies. The quality of evidence would be upgraded to moderate if we only considered estimates for carvedilol.

Similar to the other three reviews on beta blockers ([Wong 2008](#); [Wong 2014a](#); [Wong 2014b](#)), most of the studies of dual blockers did not use automated BP machines, which could have mitigated the risk of detection bias caused by loss of blinding. For this reason, the risk of detection bias remains high in this review and the quality of evidence was downgraded by one level.

Similar to the included studies of the same three reviews, none of the studies included in this review reported pulse pressure as one of their outcomes. Data for pulse pressure were not direct measurements from the studies. We calculated pulse pressure by subtracting DBP from SBP. Indirectness of this outcome was the reason that quality of evidence was further downgraded for pulse pressure to very low.

Potential biases in the review process

The rigidity of the inclusion criteria minimized the potential of bias during the selection process. Study selection was based solely on methodology. The responsibility of the review authors was to determine if the methodology fit the inclusion criteria. No other part of the studies played a role in the decision. The strict inclusion criteria ensured that included studies were well conducted in order to minimize the risk of bias during the process.

Agreements and disagreements with other studies or reviews

Two published reviews, [Chen 2010a](#) and [Law 2005](#), combined results from all subclasses of beta blockers and estimated the overall BP lowering effect of beta blockers. They did not report separate results for different subclasses of beta blockers or individual drugs. [Chen 2010a](#) also examined the additional effects of beta blockers when used as second-line treatment of hypertension. Our review examined beta blockers as first-line monotherapy for hypertension. Because of these differences, this review is not directly comparable to these reviews.

Other Cochrane reviews have compared antihypertensive drug classes with placebo and used similar inclusion and exclusion criteria to this review. Based on an indirect comparison with other classes, dual receptor blockers lowered trough BP by -6/-4 mm Hg, a smaller magnitude on average than thiazide diuretics (-9/-4 mm Hg; [Musini 2014](#)), ACE inhibitors (-8/-5 mm Hg; [Heran 2008a](#)), ARBs (-9/-6 mm Hg; [Heran 2008b](#)), and renin inhibitors (-8/-5 mm Hg; [Musini 2008](#)). Dual receptor blockers also lowered BP by a smaller magnitude than nonselective beta blockers (-10/-7 mm Hg; [Wong 2014a](#)), partial agonists (-8/-4 mm Hg; [Wong 2014b](#)) and beta1 selective beta blockers (-10/-8 mm Hg; [Wong 2008](#)). However, the difference in mean baseline BP (SBP/DBP) between dual receptor blockers and partial agonists (151/101 mm Hg versus

175/107 mm Hg) might partly explain the difference in BP lowering effect between these two subclasses. In addition, most of the included studies in the nonselective beta blocker review measured BP during peak hours while the measurements of dual receptor blocker studies were made at trough (Wong 2014a).

Like other beta blockers, the fact that dual blockers reduce DBP to an amount similar to SBP means that they have little or no effect on pulse pressure. This is similar to the other classes of beta blockers, but less than the average reduction of pulse pressure of 5 mm Hg seen with thiazides (Musini 2014) and 3 mm Hg seen with drugs inhibiting the renin angiotensin system (Heran 2008a; Heran 2008b; Musini 2008). These two differences in effect on blood pressure, little or no effect on pulse pressure and a lesser blood pressure lowering effect, might provide some insight into why first-line beta blockers do not reduce mortality and morbidity as much as first-line thiazide diuretics (Wisonge 2007; Wright 2000; Wright 2009), first-line calcium channel blockers (Chen 2010b) and first-line drugs inhibiting the renin angiotensin system (Xue 2015).

AUTHORS' CONCLUSIONS

Implications for practice

This review provides the most up-to-date evidence on the blood pressure (BP) lowering effect of dual alpha- and beta-receptor blockers. Most of the data come from patients receiving carvedilol. In patients with mild to moderate hypertension, dual blockers lowered trough BP by an average of -6/-4 mm Hg and reduced heart rate by five beats per minute. The risk of publication bias was lower for carvedilol because we found two large unpublished studies. Therefore, in this review, carvedilol provided a better estimate of BP lowering effect than the other dual blocker, labetalol. The BP lowering estimate from combining the data for starting dose (12.5 mg/day) and twice the starting dose (25 mg/day) of carvedilol is -4/-3 mm Hg. Doses higher than the starting dose did not provide a significant additional BP lowering effect.

The blood pressure lowering effect of dual alpha- and beta-receptor blockers appears to be less than non-selective, beta1 selective and partial agonist beta blockers, thiazides and drugs inhibiting the renin angiotensin system. Dual blockers also had little or no effect on reducing pulse pressure, which is similar to the other beta-blocker classes, but less than the average reduction of pulse pressure seen with thiazides and drugs inhibiting the renin angiotensin system.

Tests for dose-related differences by direct comparison were significant for heart rate. This showed that higher doses of dual blockers caused more bradycardia than lower doses.

Implications for research

1. Only a small amount of data for labetalol was publicly available. All studies should be made publicly available, including all studies that have been completed to fulfil regulatory requirements.
2. The procedure for randomization and blinding must be described in more detail in published studies.
3. All study results must be reported, including all harm data and withdrawals due to adverse effects.
4. Studies should report in more detail the method of BP measurement and time after drug administration at which BP is measured. Both peak and trough BP measurements should be reported.
5. Future reviews could assess the BP lowering effect using 24-hour ambulatory BP measurements.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Carvedilol GSK B100

Methods	Randomized, double blinded, placebo controlled. Patients entered an eight-week single blinded placebo run-in period. Eligible patients were then randomized to one of the four treatment groups. Subjects randomized to 12.5 mg and 25 mg underwent a titration period for a week, when patients were force-titrated to target doses.
Participants	Total number randomized was 480; mean age was 56 years. Inclusion criteria: sitting DBP between 95 mm Hg and 115 mm Hg. Exclusion criteria: secondary hypertension, bradycardia, second or third degree AV block, sinus syndrome, unstable angina, MI within six months, stroke within six months, CHF, arrhythmias.
Interventions	Carvedilol 6.25 mg BID, 12.5 mg BID, 25 mg BID, placebo BID.
Outcomes	Trough SBP, trough DBP, trough HR, WDAE, AE
Notes	Authors mentioned that the measurements were trough, however, they did not specify how many hours after the last dose the measurements were made.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	placebo of the same frequency was used.
Blinding of outcome assessment (detection bias) All outcomes	High risk	All beta blockers posed a risk for detection bias as the lowered HR might be detected by investigators.
Incomplete outcome data (attrition bias) Hemodynamic data	Low risk	All withdrawals were reported. ITT was used to analysis the data.
Incomplete outcome data (attrition bias) Clinical outcomes	Low risk	WDAE, AE were reported.
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported.

Carvedilol GSK B101

Methods	Randomized double blinded placebo controlled. Patients first entered an eight-week placebo run-in period for baseline assessments. Eligible patients were randomized to one of the five treatment groups for eight weeks. Subjects assigned to 12.5 mg or higher were force-titrated until target dosage was met.
Participants	Total number randomized was 520; average age was 54 years.

Carvedilol GSK B101 (Continued)

Inclusion criteria: Patients with sitting DBP between 95 mm Hg and 115 mm Hg.

Exclusion criteria: secondary hypertension, hypertensive retinopathy, bradycardia, second or third degree AV block, sick sinus syndrome, unstable angina, recent MI or stroke, CHF, arrhythmia, bronchospastic pulmonary diseases, insulin dependent diabetes, liver, renal or biliary diseases, low platelet count, low WBC counts.

Interventions	Carvedilol 6.25 mg QD, 12.5 mg QD, 25 mg QD, 50 mg QD, placebo.
Outcomes	SBP, DBP, HR, at trough hour WDAE, AE.
Notes	The authors mentioned that measurements were trough, but did not state the number of hours after the last dose that blood pressure was measured.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	placebo was used at the same frequency as treatments.
Blinding of outcome assessment (detection bias) All outcomes	High risk	All beta blockers posed a risk for detection bias as the lowered HR might be detected by investigators.
Incomplete outcome data (attrition bias) Hemodynamic data	Low risk	All withdrawals were reported. ITT was used in the analysis.
Incomplete outcome data (attrition bias) Clinical outcomes	Low risk	All withdrawals were reported.
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported.

Frick 1976

Methods	Randomized double blinded placebo cross-over study. Patients with DBP > 100 mm Hg on repeated measures were enrolled. All antihypertensive drugs were stopped for one to two months before entry. Patients were placed on treatment for four weeks and then crossed over to the other treatment.
Participants	N = 20, Baseline BP 161/113 mm Hg, Patients with DBP > 100 mm Hg during the washout period were enrolled.
Interventions	Labetalol 100 mg TID, Labetalol 200 mg TID or placebo
Outcomes	sitting SBP, DBP measured by mercury sphygmomanometer, HR.

Frick 1976 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Neither doctors nor patients were aware of the periods of active treatment."
Incomplete outcome data (attrition bias) Hemodynamic data	Unclear risk	Did not mention dropouts.
Incomplete outcome data (attrition bias) Clinical outcomes	High risk	Did not report WDAE; reported complains of patients as adverse effects.
Selective reporting (reporting bias)	High risk	Did not report WDAE.

Kane 1976

Methods	Randomized double blinded placebo controlled cross-over study. All drugs were stopped for two weeks before entry. Part I of study: one tablet was taken twice daily Part II of study: the doses were doubled. Each part contained two four-week periods, alternated between treatment and placebo.
Participants	N = 30, baseline BP 169/107 mm Hg. Patients under 65 years of age with DBP between 95 and 120 mm Hg were enrolled.
Interventions	labetalol 200 mg BID, 400 mg BID or placebo
Outcomes	sitting SBP, DBP measured by mercury sphygmomanometer, HR.
Notes	
Risk of bias	

Kane 1976 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly allocated by a double blind code."
Allocation concealment (selection bias)	Low risk	"labetalol or placebo tablets of identical appearance."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"labetalol or placebo tablets of identical appearance."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Did not use automated machine.
Incomplete outcome data (attrition bias) Hemodynamic data	Low risk	All dropouts were accounted for and were not included in the analyses.
Incomplete outcome data (attrition bias) Clinical outcomes	Low risk	WDAE were reported.
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported.

Lechi 1982

Methods	Patients entered into a two-week placebo washout period, then eligible patients entered into four cross-over treatment cycles, each lasting three weeks.	
Participants	32 patients (22 males) aged from 30 to 63 years, with WHO stage I or II primary hypertension. Inclusion: Baseline BP 156/106 mm Hg. Exclusion: bradycardia, hypokalemia, body weight more than 20% above ideal, pregnant women, gout, asthma, COPD, collagen diseases, rheumatoid arthritis, diabetes mellitus, neoplasm and liver diseases.	
Interventions	Labetalol 100 mg TID, Chlorthalidone 10 mg TID, Labetalol 100 mg + Chlorthalidone 10 mg TID, placebo TID.	
Outcomes	SBP, DBP, HR, blood chemistry	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The trial design was Latin square.... The square was assigned at random to the various centres."
Allocation concealment (selection bias)	Low risk	"All drugs were administrated double blind"

Lechi 1982 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All drugs were administrated double blind"
Blinding of outcome assessment (detection bias) All outcomes	High risk	All beta blockers posed a risk for detection bias as the lowered HR might be detected by investigators.
Incomplete outcome data (attrition bias) Hemodynamic data	High risk	One patients withdrew from the study due to adverse effects. However, the authors did not report the group to which that patient had been assigned.
Incomplete outcome data (attrition bias) Clinical outcomes	High risk	One patient withdrew due to adverse effects. However, the authors did not report to which group the patient had been assigned.
Selective reporting (reporting bias)	Low risk	All hemodynamic outcomes reported. WDAE report was incomplete.

McPhillips 1988

Methods	Patients entered a four-week placebo run-in period. Eligible patients were then randomized to one of the four parallel treatment groups for four weeks. All interventions were administrated double blinded. At the end of the run-in and treatment periods, patients were admitted to the clinical research unit for a 30-hour observation period.	
Participants	92 patients were screened and 44 patients qualified for the treatment period. 34 of the 44 eligible were male; mean age of all four groups ranged from 44.3 to 56.1 years. Their baseline supine DBP was 99.1 mm Hg.	
Interventions	Carvedilol 12.5mg QD, 25mg QD, 50mg QD, placebo	
Outcomes	SBP, DBP, HR, C _{max} , serum half life.	
Notes	The baseline age of each group was different.	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was used.
Blinding of outcome assessment (detection bias)	High risk	All beta blockers posed a risk for detection bias as the lowered HR might be detected by investigators.

Blood pressure lowering efficacy of dual alpha and beta blockers for primary hypertension (Review)

McPhillips 1988 (Continued)

All outcomes

Incomplete outcome data (attrition bias) Hemodynamic data	Low risk	Total withdrawal data were reported. The patients who withdrew were not included in the analysis.
Incomplete outcome data (attrition bias) Clinical outcomes	Low risk	Total withdrawal and safety data reported
Selective reporting (reporting bias)	High risk	HR of each group at the end of the treatment was not reported

Rouffy 1986

Methods	After a 30-day run-in period, eligible patients were randomized to a double blinded parallel treatment period for three months.
Participants	30 patients with a mean age of 45 years; range from 34 to 57 years. Inclusion: Baseline BP 174/98 mm Hg. Exclusion: CVD, taking lipid modifying drugs, contraindicated for beta blockers, obesities, abnormal glycemic level, consumption of more than 250 g of alcohol per week and patients whose life styles changed during the study.
Interventions	Labetalol 200mg BID, placebo
Outcomes	SBP, DBP, HR, lipid, lipoprotein
Notes	Study is in French.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was used for the study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	All beta blockers posed a risk for detection bias as the lowered HR might be detected by investigators.
Incomplete outcome data (attrition bias) Hemodynamic data	High risk	One patients lost to follow-up but their data were included in the analysis
Incomplete outcome data (attrition bias)	High risk	One patients lost to follow-up but their data were included in the analysis

Blood pressure lowering efficacy of dual alpha and beta blockers for primary hypertension (Review)

Rouffy 1986 (Continued)

Clinical outcomes

Selective reporting (reporting bias)	Low risk	All outcomes reported.
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Weber 2006

Methods	After a four-week run-in period, eligible subjects were randomized to one of the four treatment groups for eight weeks. Patients who were randomized to 40 mg or 80 mg groups were force-titrated to the dose within four weeks.
Participants	Total number of 337 subjects were recruited. 20 mg N = 87, 40 mg N = 78, 80 mg N = 88, placebo N = 84. Baseline BP 150.7/99 mm Hg.
Interventions	Carvedilol CR 20 mg QD, Carvedilol CR 40 mg QD, Carvedilol CR 80 mg QD and placebo
Outcomes	Office & ABPM SBP, DBP, HR (trough measurement at 20 to 24 hr after last dose), safety and withdrawals.
Notes	Patients randomized to Carvedilol CR 80 mg/day were only on 80 mg for two weeks, therefore, the data did not meet the inclusion criteria.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Each dose level of active carvedilol CR had a matching placebo."
Blinding of outcome assessment (detection bias) All outcomes	High risk	All beta blockers posed a risk for detection bias as the lowered HR might be detected by investigators.
Incomplete outcome data (attrition bias) Hemodynamic data	Low risk	Patients who dropout were reported and not included in the analysis.
Incomplete outcome data (attrition bias) Clinical outcomes	Low risk	All withdrawal were reported and accounted for.
Selective reporting (reporting bias)	Low risk	Authors reported all hemodynamic data and all safety and withdrawal data.

SBP - systolic blood pressure
DBP - diastolic blood pressure
mm Hg - millimeters of mercury

TID - three times a day
BID - twice a day
QD - each day; daily
AV block - atrial ventricular block
MI - myocardial infarction
WDAE - withdrawal due to adverse effects
AE - adverse effects
HR - heart rate
ITT - intention to treat analysis
C_{max} - maximum (or peak) serum concentration after a drug has been administered
CR - controlled-release
ABPM - Automatic blood pressure monitor
hr - hour

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Dupont 1987	Did not report placebo group data
Horvath 1979	Report on MAP
Kubik 1984	Authors claimed to have placebo controlled. But all patients took placebo during first four weeks of treatment. Then patients were randomly assigned to three active treatment arms. The period during which patients took placebo was not random.
Wilcox 1978	Patients were randomized to four-week treatment periods. However, during each period, the drugs were taken at two doses. Each dose only lasted for two weeks.

MAP - mean arterial pressure

DATA AND ANALYSES

Comparison 1. Carvedilol vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 systolic blood pressure	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 (0.5 initial) 6.25 mg/day	1	236	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-5.20, 3.40]
1.2 (initial dose) 12.5 mg/day	3	494	Mean Difference (IV, Fixed, 95% CI)	-3.53 [-6.38, -0.68]
1.3 (2x initial) 20 & 25 mg/day	4	644	Mean Difference (IV, Fixed, 95% CI)	-4.09 [-6.52, -1.65]
1.4 (4x initial) 40 & 50 mg/day	4	527	Mean Difference (IV, Fixed, 95% CI)	-6.51 [-9.35, -3.66]
2 diastolic blood pressure	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 (0.5 initial) 6.25 mg/day	1	236	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-3.06, 1.66]
2.2 (initial dose) 12.5 mg/day	3	494	Mean Difference (IV, Fixed, 95% CI)	-2.26 [-3.88, -0.63]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 (2x initial) 20 & 25 mg/day	4	644	Mean Difference (IV, Fixed, 95% CI)	-2.99 [-4.38, -1.60]
2.4 (4x initial) 40 & 50 mg/day	4	527	Mean Difference (IV, Fixed, 95% CI)	-5.04 [-6.64, -3.44]
3 Heart rate	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 (0.5 initial) 6.25 mg/day	1	236	Mean Difference (IV, Fixed, 95% CI)	-1.4 [-3.89, 1.09]
3.2 (initial dose) 12.5 mg/day	2	474	Mean Difference (IV, Fixed, 95% CI)	-2.15 [-3.86, -0.43]
3.3 (2x initial) 20 & 25 mg/day	3	624	Mean Difference (IV, Fixed, 95% CI)	-4.68 [-6.05, -3.31]
3.4 (4x initial) 40 & 50 mg/day	3	506	Mean Difference (IV, Fixed, 95% CI)	-6.33 [-7.93, -4.74]
4 Pulse pressure	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 (0.5 initial) 6.25 mg/day	1	236	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-3.93, 3.53]
4.2 (initial dose) 12.5 mg/day	3	494	Mean Difference (IV, Fixed, 95% CI)	-1.24 [-3.72, 1.23]
4.3 (2x initial) 20 & 25 mg/day	4	644	Mean Difference (IV, Fixed, 95% CI)	-1.19 [-3.32, 0.93]
4.4 (4x initial) 40 & 50 mg/day	4	527	Mean Difference (IV, Fixed, 95% CI)	-1.58 [-4.06, 0.91]

Analysis 1.1. Comparison 1 Carvedilol vs placebo, Outcome 1 systolic blood pressure.

Analysis 1.2. Comparison 1 Carvedilol vs placebo, Outcome 2 diastolic blood pressure.

Analysis 1.3. Comparison 1 Carvedilol vs placebo, Outcome 3 Heart rate.

Analysis 1.4. Comparison 1 Carvedilol vs placebo, Outcome 4 Pulse pressure.

Comparison 2. Labetalol vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 systolic blood pressure	4		Mean Difference (Fixed, 95% CI)	Subtotals only
1.1 (2x initial) 300 & 400 mg/day	4	110	Mean Difference (Fixed, 95% CI)	-10.36 [-13.95, -6.77]
1.2 (4x initial) 600 & 800 mg/day	2	44	Mean Difference (Fixed, 95% CI)	-19.69 [-25.38, -13.99]
2 diastolic blood pressure	4		Mean Difference (Fixed, 95% CI)	Subtotals only
2.1 (2x initial) 300 & 400 mg/day	4	110	Mean Difference (Fixed, 95% CI)	-6.59 [-8.60, -4.58]
2.2 (4x initial) 600 & 800 mg/day	2	44	Mean Difference (Fixed, 95% CI)	-14.58 [-18.02, -11.15]
3 Heart rate	4		Mean Difference (Fixed, 95% CI)	Subtotals only
3.1 (2x initial) 300 & 400 mg/day	4	110	Mean Difference (Fixed, 95% CI)	-7.07 [-9.13, -5.01]
3.2 (4x initial) 600 & 800 mg/day	2	44	Mean Difference (Fixed, 95% CI)	-7.67 [-10.43, -4.91]
4 Pulse pressure	4		Mean Difference (Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 (2x initial) 300 & 400mg/day	4	110	Mean Difference (Fixed, 95% CI)	-3.59 [-6.73, -0.46]
4.2 (4x initial) 600 & 800 mg/day	2	44	Mean Difference (Fixed, 95% CI)	-4.64 [-9.65, 0.37]

Analysis 2.1. Comparison 2 Labetalol vs placebo, Outcome 1 systolic blood pressure.

Analysis 2.2. Comparison 2 Labetalol vs placebo, Outcome 2 diastolic blood pressure.

Study or subgroup	labetalol	placebo	Mean Dif- ference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
	N	N				
Test for overall effect: $Z=8.33(P<0.0001)$						
<div style="display: flex; justify-content: space-between;"> Favours labetalol -20 -10 0 10 20 Favours placebo </div>						

Analysis 2.3. Comparison 2 Labetalol vs placebo, Outcome 3 Heart rate.

Study or subgroup	labetalol	placebo	Mean Dif- ference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
	N	N				
2.3.1 (2x initial) 300 & 400 mg/day						
Frick 1976	20	0	-6 (3)		12.29%	-6[-11.88,-0.12]
Kane 1976	28	0	-8 (1.99)		27.92%	-8[-11.9,-4.1]
Lechi 1982	32	0	-8 (1.73)		36.95%	-8[-11.39,-4.61]
Rouffy 1986	20	10	-5 (2.2)		22.85%	-5[-9.31,-0.69]
Subtotal (95% CI)					100%	-7.07[-9.13,-5.01]
Heterogeneity: $\tau^2=0$; $\chi^2=1.52$, $df=3(P=0.68)$; $I^2=0\%$						
Test for overall effect: $Z=6.72(P<0.0001)$						
2.3.2 (4x initial) 600 & 800 mg/day						
Frick 1976	20	0	-6 (3.46)		16.53%	-6[-12.78,0.78]
Kane 1976	24	0	-8 (1.54)		83.47%	-8[-11.02,-4.98]
Subtotal (95% CI)					100%	-7.67[-10.43,-4.91]
Heterogeneity: $\tau^2=0$; $\chi^2=0.28$, $df=1(P=0.6)$; $I^2=0\%$						
Test for overall effect: $Z=5.45(P<0.0001)$						
<div style="display: flex; justify-content: space-between;"> Favours labetalol -10 -5 0 5 10 Favours placebo </div>						

Analysis 2.4. Comparison 2 Labetalol vs placebo, Outcome 4 Pulse pressure.

Study or subgroup	labetalol	placebo	Mean Dif- ference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
	N	N				
2.4.1 (2x initial) 300 & 400mg/day						
Frick 1976	20	0	-3 (3.3)		23.49%	-3[-9.47,3.47]
Kane 1976	28	0	-9 (4.2)		14.5%	-9[-17.23,-0.77]
Lechi 1982	32	0	-2 (3.04)		27.68%	-2[-7.96,3.96]
Rouffy 1986	20	10	-3 (2.73)		34.32%	-3[-8.35,2.35]
Subtotal (95% CI)					100%	-3.59[-6.73,-0.46]
Heterogeneity: $\tau^2=0$; $\chi^2=2.01$, $df=3(P=0.57)$; $I^2=0\%$						
Test for overall effect: $Z=2.25(P=0.02)$						
2.4.2 (4x initial) 600 & 800 mg/day						
Frick 1976	20	0	-4 (3.1)		67.91%	-4[-10.08,2.08]
Kane 1976	24	0	-6 (4.51)		32.09%	-6[-14.84,2.84]
Subtotal (95% CI)					100%	-4.64[-9.65,0.37]
Heterogeneity: $\tau^2=0$; $\chi^2=0.13$, $df=1(P=0.71)$; $I^2=0\%$						
Test for overall effect: $Z=1.82(P=0.07)$						
<div style="display: flex; justify-content: space-between;"> Favours labetalol -20 -10 0 10 20 Favours placebo </div>						

Comparison 3. Pooled overall effects

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 systolic blood pressure	8		Mean Difference (Fixed, 95% CI)	Subtotals only
1.1 0.5x initial doses	1	236	Mean Difference (Fixed, 95% CI)	-0.90 [-5.19, 3.39]
1.2 1x initial doses	3	494	Mean Difference (Fixed, 95% CI)	-3.53 [-6.38, -0.69]
1.3 2x initial doses	8	754	Mean Difference (Fixed, 95% CI)	-6.06 [-8.08, -4.05]
1.4 4x initial doses	6	571	Mean Difference (Fixed, 95% CI)	-9.16 [-11.73, -6.60]
2 diastolic blood pressure	8		Mean Difference (Fixed, 95% CI)	Subtotals only
2.1 0.5x initial doses	1	236	Mean Difference (Fixed, 95% CI)	-0.7 [-3.05, 1.65]
2.2 1x initial doses	3	494	Mean Difference (Fixed, 95% CI)	-2.26 [-3.88, -0.64]
2.3 2x initial doses	8	754	Mean Difference (Fixed, 95% CI)	-4.16 [-5.30, -3.01]
2.4 4x initial doses	6	571	Mean Difference (Fixed, 95% CI)	-6.74 [-8.19, -5.29]
3 Heart rate	7		Mean Difference (Fixed, 95% CI)	Subtotals only
3.1 0.5x initial doses	1	237	Mean Difference (Fixed, 95% CI)	-1.4 [-3.89, 1.09]
3.2 1x initial doses	2	474	Mean Difference (Fixed, 95% CI)	-2.14 [-3.85, -0.43]
3.3 2x initial doses	7	734	Mean Difference (Fixed, 95% CI)	-5.41 [-6.56, -4.27]
3.4 4x initial doses	5	550	Mean Difference (Fixed, 95% CI)	-6.67 [-8.05, -5.29]
4 Pulse Pressure	8		Mean Difference (Fixed, 95% CI)	Subtotals only
4.1 0.5x initial doses	1	236	Mean Difference (Fixed, 95% CI)	-0.2 [-3.92, 3.52]
4.2 1x initial doses	3	494	Mean Difference (Fixed, 95% CI)	-1.25 [-3.73, 1.23]
4.3 2x initial doses	8	754	Mean Difference (Fixed, 95% CI)	-2.19 [-4.01, -0.37]
4.4 4x initial doses	6	571	Mean Difference (Fixed, 95% CI)	-2.43 [-5.18, 0.31]
5 withdrawal due to adverse effects	5	1412	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.54, 1.42]

Analysis 3.1. Comparison 3 Pooled overall effects, Outcome 1 systolic blood pressure.

Analysis 3.2. Comparison 3 Pooled overall effects, Outcome 2 diastolic blood pressure.

Analysis 3.3. Comparison 3 Pooled overall effects, Outcome 3 Heart rate.

Analysis 3.4. Comparison 3 Pooled overall effects, Outcome 4 Pulse Pressure.

Analysis 3.5. Comparison 3 Pooled overall effects, Outcome 5 withdrawal due to adverse effects.

Comparison 4. Adjusted combined once and twice starting dose effects

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 systolic blood pressure	8	1007	Mean Difference (Fixed, 95% CI)	-5.59 [-7.47, -3.70]
1.1 1x initial doses	3	374	Mean Difference (Fixed, 95% CI)	-3.51 [-7.09, 0.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 2x initial doses	8	633	Mean Difference (Fixed, 95% CI)	-6.39 [-8.61, -4.16]
2 diastolic blood pressure	8	1007	Mean Difference (Fixed, 95% CI)	-3.88 [-4.95, -2.82]
2.1 1x initial doses	3	374	Mean Difference (Fixed, 95% CI)	-2.26 [-4.29, -0.24]
2.2 2x initial doses	8	633	Mean Difference (Fixed, 95% CI)	-4.50 [-5.75, -3.25]
3 Heart rate	7	977	Mean Difference (Fixed, 95% CI)	-4.62 [-5.71, -3.54]
3.1 1x initial doses	2	359	Mean Difference (Fixed, 95% CI)	-2.16 [-4.28, -0.04]
3.2 2x initial doses	7	618	Mean Difference (Fixed, 95% CI)	-5.50 [-6.77, -4.24]
4 Pulse Pressure	8	1007	Mean Difference (Fixed, 95% CI)	-1.89 [-3.58, -0.20]
4.1 1x initial doses	3	374	Mean Difference (Fixed, 95% CI)	-1.22 [-4.32, 1.88]
4.2 2x initial doses	8	633	Mean Difference (Fixed, 95% CI)	-2.17 [-4.19, -0.15]

Analysis 4.1. Comparison 4 Adjusted combined once and twice starting dose effects, Outcome 1 systolic blood pressure.

Analysis 4.2. Comparison 4 Adjusted combined once and twice starting dose effects, Outcome 2 diastolic blood pressure.

Analysis 4.3. Comparison 4 Adjusted combined once and twice starting dose effects, Outcome 3 Heart rate.

Analysis 4.4. Comparison 4 Adjusted combined once and twice starting dose effects, Outcome 4 Pulse Pressure.

APPENDICES

Appendix 1. 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 deacetylmepipranolol: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 bevantolol.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 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 search strategy

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

Protocol first published: Issue 4, 2008
Review first published: Issue 8, 2015

Date	Event	Description
18 June 2010	Amended	Added second author, amended inclusion criteria to accept crossover studies; added double blind to inclusion criteria. Updated background and search methods.

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.

Alexandra Laugerrotte confirmed the data as second reviewer.

DECLARATIONS OF INTEREST

Gavin Wong: Nothing to declare.

Alexandra Laugerrotte: Nothing to declare.

James M Wright: 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 alpha-1 Receptor Antagonists [*therapeutic use]; Adrenergic beta-Antagonists [*therapeutic use]; Antihypertensive Agents [*therapeutic use]; Blood Pressure [*drug effects]; Carbazoles [therapeutic use]; Carvedilol; Essential Hypertension; Heart Rate [drug effects]; Hypertension [*drug therapy]; Labetalol [therapeutic use]; Propanolamines [therapeutic use]; Randomized Controlled Trials as Topic; Withholding Treatment

MeSH check words

Humans