Cochrane Library

Cochrane Database of Systematic Reviews

Blood pressure lowering efficacy of beta-1 selective beta blockers for primary hypertension (Review)

Wong GWK, Boyda HN, Wright JM

Wong GWK, Boyda HN, Wright JM.
Blood pressure lowering efficacy of beta-1 selective beta blockers for primary hypertension.
Cochrane Database of Systematic Reviews 2016, Issue 3. Art. No.: CD007451.
DOI: 10.1002/14651858.CD007451.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Blood pressure lowering efficacy of beta-1 selective beta blockers for primary hypertension

Gavin WK Wong[1], Heidi N Boyda[1], James M Wright[1]

[1]Department 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: Edited (no change to conclusions), comment added to review, published in Issue 4, 2016.

Citation: Wong GWK, Boyda HN, Wright JM. Blood pressure lowering efficacy of beta-1 selective beta blockers for primary hypertension. *Cochrane Database of Systematic Reviews* 2016, Issue 3. Art. No.: CD007451. DOI: 10.1002/14651858.CD007451.pub2.

ABSTRACT

Background

Beta blockers are commonly used to treat hypertension. The blood pressure reading is the primary tool for physicians and patients to assess the efficacy of the treatment. The blood pressure lowering effect of beta-1 selective blockers is not known.

Objectives

To quantify the dose-related effects of various doses and types of beta-1 selective adrenergic receptor blockers on systolic and diastolic blood pressure versus placebo in people with primary hypertension.

Search methods

We searched the Database of Abstracts of Reviews of Effectiveness (DARE) for related reviews.

We searched the following databases for primary studies: the Cochrane Hypertension Specialised Register (All years to 15 October 2015), CENTRAL via the Cochrane Register of Studies Online (2015, Issue 10), Ovid MEDLINE (1946 to 15 October 2015), Ovid EMBASE (1974 to 15 October 2015) and ClinicalTrials.gov (all years to 15 October 2015).

The Hypertension Group Specialised Register includes controlled trials from searches of CAB Abstracts, CINAHL, Cochrane Central Register of Controlled Trials, EMBASE, Food Science and Technology Abstracts (FSTA), Global Health, LILACS, MEDLINE, ProQuest Dissertations & Theses, PsycINFO, Web of Science and the WHO International Clinical Trials Registry Platform (ICTRP).

Electronic databases were searched using a strategy combining the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision) with selected MeSH terms and free text terms. No language restrictions were used. The MEDLINE search strategy was translated into CENTRAL, EMBASE, the Hypertension Group Specialised Register and ClinicalTrials.gov using the appropriate controlled vocabulary as applicable. Full strategies are in Appendix 1.

Selection criteria

Randomised, double-blind, placebo-controlled parallel or cross-over trials. Studies had to contain a beta blocker monotherapy arm with fixed dose. People enrolled into the studies had to have primary hypertension at baseline. Duration of studies had to be between 3 weeks to 12 weeks. Drugs in this class of beta blockers are atenolol, betaxolol, bevantolol, bisoprolol, esmolol, metoprolol, nebivolol, pafenolol, practolol.

Data collection and analysis

Two authors confirmed the inclusion of studies and extracted the data independently. Review Manager (RevMan) 5.3.5 was used to synthesise data.

Main results

We identified 56 RCTs (randomised controlled trials) that examined the blood pressure (BP) lowering efficacy of beta-1 selective blockers (beta-1 blocker) in 7812 primary hypertensive patients. Among the included trials, 26 RCTs were parallel studies and 30 RCTs were cross-over studies, examining eight beta-1 blockers. Overall, the majority of beta-1 blockers studied significantly lowered systolic blood pressure (SBP) and diastolic blood pressure (DBP). In people with mild to moderate hypertension, beta-1 selective blockers lowered BP by an average of -10/-8 mmHg and reduced heart rate by 11 beats per minute. The maximum BP reduction of beta-1 blockers occurred at twice the starting dose. Individual beta-1 blockers did not exhibit a graded dose-response effect on SBP and DBP over the recommended dose range.

Most beta-1 blockers tested significantly lowered heart rate. A graded dose-response of beta-1 blockers on heart rate was evident. Higher dose beta-1 blockers lowered heart rate more than lower doses. Individually and overall beta-1 blockers did not affect pulse pressure, which distinguishes them from other classes of drugs.

Authors' conclusions

This review provides low quality evidence that in people with mild to moderate hypertension, beta-1 selective blockers lowered BP by an average of -10/-8 mmHg and reduced heart rate by 11 beats per minute as compared to placebo. The effect of beta-1 blockers at peak hours, -12/-9 mmHg, was greater than the reduction at trough hours, -8/-7 mmHg. Beta-1 selective blockers lowered BP by a greater magnitude than dual receptor beta-blockers and partial agonist beta-blockers, lowered BP similarly to nonselective beta-blockers. Beta-1 selective blockers lowered SBP by a similar degree and lowered DBP by a greater degree than diuretics, angiotensin converting enzyme inhibitors and angiotensin receptor blockers. Because DBP is lowered by a similar extent to SBP, beta-1 selective blockers do not reduce pulse pressure.

PLAIN LANGUAGE SUMMARY

Beta-1 selective blockers for treatment of high blood pressure

Background

Beta-1 selective blockers are a subclass of beta blockers that are commonly used to treat high blood pressure. Drugs in this class include atenolol (Tenormin), metoprolol (Lopressor), nebivolol (Bystolic) and bisoprolol (Zebeta, Monocor). We developed a comprehensive methodology to examine how different doses and drugs in this class of drugs lower blood pressure.

Characteristics of included studies

We found and included 56 clinical trials examining the blood pressure lowering effect of eight beta-1 blockers in 7812 people with high blood pressure. These participants were randomly assigned to receive a fixed dose of beta-1 blocker treatment or placebo for 3 weeks to 12 weeks.

Key results

On average, beta-1 blockers lowered BP by -10 points of systolic and -8 points of diastolic pressure in people with mild to moderate high blood pressure. In general, higher doses of beta-1 blockers did not show greater reduction of blood pressure compared to lower doses. The maximum blood pressure reduction was exhibited at twice the recommended starting dose.

Higher doses of beta-1 blockers lowered heart rate more than the lower doses, therefore are more likely to cause the common side effect of slowed heart rate. Beta-1 selective blockers lower systolic and diastolic BP to a similar degree, as is the case for the other subclasses of beta blockers, and thus have little or no effect on pulse pressure. This is different from other classes of antihypertensive drugs, such as thiazide diuretics, angiotensin converting enzyme inhibitors and angiotensin receptor blockers.

Quality of 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.

Blood pressure lowering effects of beta-1 blockers compared with placebo for primary hypertension

Patient or population: People with primary hypertension

Intervention: Beta-1 selective blockers

Comparison: Placebo

Outcomes	mean estimates of combining 1x and 2x starting dose (95% CI)	No of Participants (No. of RCT)	Quality of the evidence (GRADE)
Systolic blood pressure	-10.4 (-11.1, -9.7)[1,2,3]	5246 (47)	Low[4,5]
Diastolic blood pressure	-8.3 (-8.7, -7.8)[1,2,3]	5316 (48)	Low[4,5]
Heart rate	-10.9 (-11.5, -10.4)[1,2]	3407 (33)	Low[4,5]
Pulse pressure	-1.8 [-2.3, -1.2][1,2]	5246 (47)	Very low[4,5,6]
WDAE	0.9 (0.5, 1.5)	2618 (3)	Low[7,8]

95% CI: 95% confident interval; WDAE: Withdrawal due to adverse effect.

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 data for this analysis is from recommended starting and 2x the starting dose. Combining them provides the best estimate of the subclass effect.
2. Half of measurements at peak hours and the other half at trough hours.
3. The mean baseline BP was 156/101 mmHg.
4. Downgraded due to publication bias, extreme outliers causing significant heterogeneity within some subgroups.
5. Downgraded due to high risk of detection bias caused by loss of blinding.
6. Downgraded due to indirectness, none of the studies reported pulse pressure. Pulse pressure was calculated by subtracting DBP from SBP.
7. Downgraded due to imprecision.
8. Downgraded due to selective reporting bias.

BACKGROUND

Description of the condition

Elevated blood pressure (hypertension) 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 such class of drug.

Description of the intervention

Beta-blockers were originally marketed and used to treat angina. During their use in people with angina, it was discovered that they also lowered blood pressure. Since then, they have received clinical attention because of their established effectiveness for certain arrhythmias and their known preventative action in people who have had a myocardial infarction.

Five previous 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, significantly reduced total mortality as compared to placebo, whereas beta-1 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 2012). This review concluded that beta blockers were not the best class of drugs to use as first-line antihypertensive therapy. However, it is possible that this related to beta-1 selective beta blockers, as atenolol was the beta-blocker used in 75% of the trials.

Three 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 decreased 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 given as a second-line drug did not differentiate between the different classes of beta-blockers (Chen 2010).

How the intervention might work

Beta adrenergic receptors are present in many peripheral 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 beta-receptors and thus modulate sympathetic nervous system activity. There are three main classes of beta-receptors: beta-1, beta-2 and beta-3. Beta-1 (cardioselective) receptor blockers have a greater specificity to block beta-1 receptors than beta-2 receptors. However, this selectivity diminishes as the dose of the beta-blocker increases. Drugs in this class have no intrinsic sympathomimetic activity (partial agonist) or alpha blocking effects. Beta-1 adrenergic receptors are the predominant adrenergic receptor in the heart. Activation of beta-1 receptors opens L-type calcium channels through the cAMP/protein kinase A pathway. Opening of L-type calcium channels allows calcium ions to flow into the cells and produce a positive inotropic and chronotropic effect (Kamp 2000). Blocking of beta-1 receptors decreases heart rate and cardiac contractility. This effect could contribute to the antihypertensive effect of beta-1 blockers (Westfall 2011).

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 measurement is used on a daily basis by physicians managing people with high blood pressure, it is important to accurately assess the average magnitude of blood pressure lowering effects of beta blockers both individually and as sub-classes. The findings of this review will be compared to the results of the Cochrane reviews of the other the subclasses of beta blockers: non-selective beta blockers (Wong 2014a), partial agonist beta blockers (Wong 2014b) dual alpha and beta blockers (Wong 2015). 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 of various doses and types of beta-1 selective adrenergic receptor blockers on systolic and diastolic blood pressure versus placebo in people with primary hypertension.

Secondary objectives

1. To determine the effects of beta-1 selective adrenergic receptor blockers on variability of blood pressure.
2. To determine the effects of beta-1 selective adrenergic receptor blockers on pulse pressure.
3. To quantify the dose-related effects of beta-1 selective adrenergic receptor blockers on heart rate.
4. To quantify the effects of beta-1 selective adrenergic receptor blockers at various doses on withdrawals due to adverse events.

METHODS

Criteria for considering studies for this review

Types of studies

Study design must meet the following criteria:

1. placebo-controlled;
2. random allocation to beta adrenergic receptor blocker group and placebo group;
3. parallel or cross-over design;
4. double-blinded;
5. duration of follow-up of at least three weeks;
6. blood pressure measurements at baseline (following washout) and at one or more time points between 3 weeks to 12 weeks after starting treatment.

Types of participants

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

Types of interventions

Monotherapy with any beta-1 selective adrenergic receptor blocker, including atenolol, betaxolol, bevantolol, bisoprolol, esmolol, metoprolol and nebivolol, pafenolol, practolol.

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 hours to 26 hours after the dose) or peak (1 hour 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, we used the mean differences (MD) of blood pressures taken in the 3 week to 12 week range.

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 participants who withdrew due to adverse events compared to placebo.

Search methods for identification of studies

Electronic searches

We searched the Hypertension Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (2015 Issue 9), Ovid MEDLINE (1946 to October 2015), Ovid EMBASE (1974 to October 2015) and ClinicalTrials.gov (all years to October 2015) for randomised controlled trials. We searched the Database of Abstracts of Reviews of Effects (DARE) for related reviews (October 2015). No language restrictions were applied. The WHO International Clinical Trials Registry Platform (ICTRP) is searched for inclusion in the Group's Specialised Register.

We used 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 to identify the relevant articles. The MEDLINE strategy was translated into CENTRAL, EMBASE, ClinicalTrials.gov, and the Hypertension Group Specialised Register (Appendix 1) .

Searching other resources

We used previously published meta-analyses on dose-response of beta adrenergic receptor blockers to help identify references to trials.

We searched the bibliographies of pertinent articles, reviews and texts for additional citations.

Data collection and analysis

Selection of studies

We performed the initial search of all the databases to identify citations with potential relevance. The initial screen of these abstracts excluded articles whose titles or abstracts, or both were clearly irrelevant. We retrieved the full text of the remaining articles and translated them into English where required. We imported the references and abstracts identified by our search into Reference Manager 11 software. Two independent reviewers assessed the eligibility of the trials using a trial selection form based on the criteria listed above. 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 (Higgins 2011a). 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, we used data reported from any single position, 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, we used standing blood pressure. We reported effect measures as the mean difference (MD) in BP, heart rate and pulse pressure between the treatment and placebo groups with 95% confidence interval (CI). We reported risk ratio (RR) 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 tested for heterogeneity of treatment effect between the trials using a standard Chi^2 statistic for heterogeneity. We applied the fixed-effect model to obtain summary statistics of pooled trials, unless significant between-study heterogeneity was present, in which case we used the random-effects model (Deeks 2011).

Data synthesis

We carried out data synthesis and analysis using the Cochrane Review Manager software, RevMan 5.3.5 (RevMan 2014).

We combined data for changes in blood pressure and heart rate using mean difference (MD). We analysed drop-outs due to side effects by using risk ratio (RR). When we found statistically significant RR, we calculated risk difference (RD), and number needed to treat for an additional harmful outcome (NNTH).

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 2011b) to calculate the standard deviation of the difference between treatment and placebo. In order to minimise the loss of statistical power for the estimates we did not adjust the standard error and sample sizes shown in the 'Data and analyses' tables for subgroup comparisons. To avoid double counting of participants 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. gender, age and race;
3. co-morbid conditions: ischaemic heart disease, peripheral vascular disease, diabetes;
4. baseline severity of hypertension: mild, moderate, severe.

Sensitivity analysis

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

1. trials that were 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.

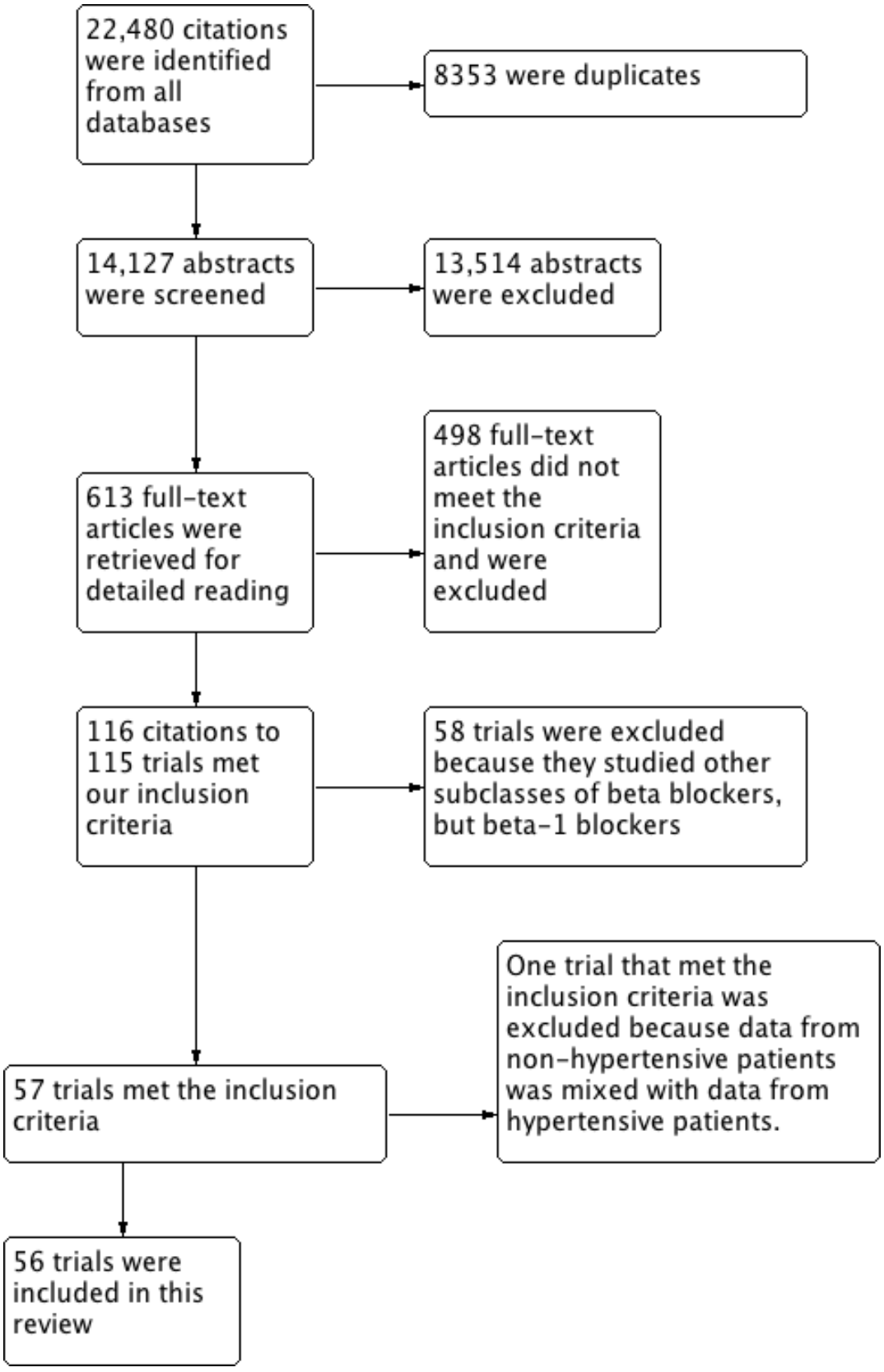
RESULTS

Description of studies

Results of the search

In order to save time and effort, the trial search coordinator from Cochrane Hypertension group developed a comprehensive search strategy (Appendix 1) so that all four subclasses of beta blockers were searched simultaneously. We used the same study inclusion criteria for the other three beta blocker reviews (Wong 2014a; Wong 2014b; Wong 2015). Citations were then sorted according to their respective subclasses afterward. Please refer to Figure 1 for the flow diagram of study selection.

Figure 1. PRISMA study flow diagram



The search was first run in May 2010, and subsequent searches have been performed up to October 2015. A total of 22,480 citations have been identified in all searches since May 2010, of which 8353 were confirmed to be duplicates. The reviewers then screened 14,127 titles and abstracts, of which 13,514 citations were excluded. We judged 613 citations to potentially meet the inclusion criteria based on title and abstract and retrieved them for detailed review. We excluded 498 full text articles which did not meet our inclusion criteria. One hundred and fifteen trials met our inclusion criteria for all four subclasses. In total, 56 trials were included in this review.

Included studies

We included 56 RCTs that examined the BP lowering efficacy of eight beta-1 blockers in 7812 primary hypertensive patients. Twenty six RCTs were parallel studies and the other 30 RCTs were cross-over studies with duration of treatment ranging from 3 weeks to 16 weeks. When study duration was longer than 12 weeks, we used only the data obtained between 3 weeks to 12 weeks. The mean baseline BP of the randomised participants in the studies was 155.6/101.1 mmHg. Please refer to Characteristics of included studies for details of included studies.

Excluded studies

We excluded one RCT that met the inclusion criteria because it reported data from non-hypertensive participants mixed with hypertensive participants. This RCT was listed in the Characteristics of excluded studies.

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.

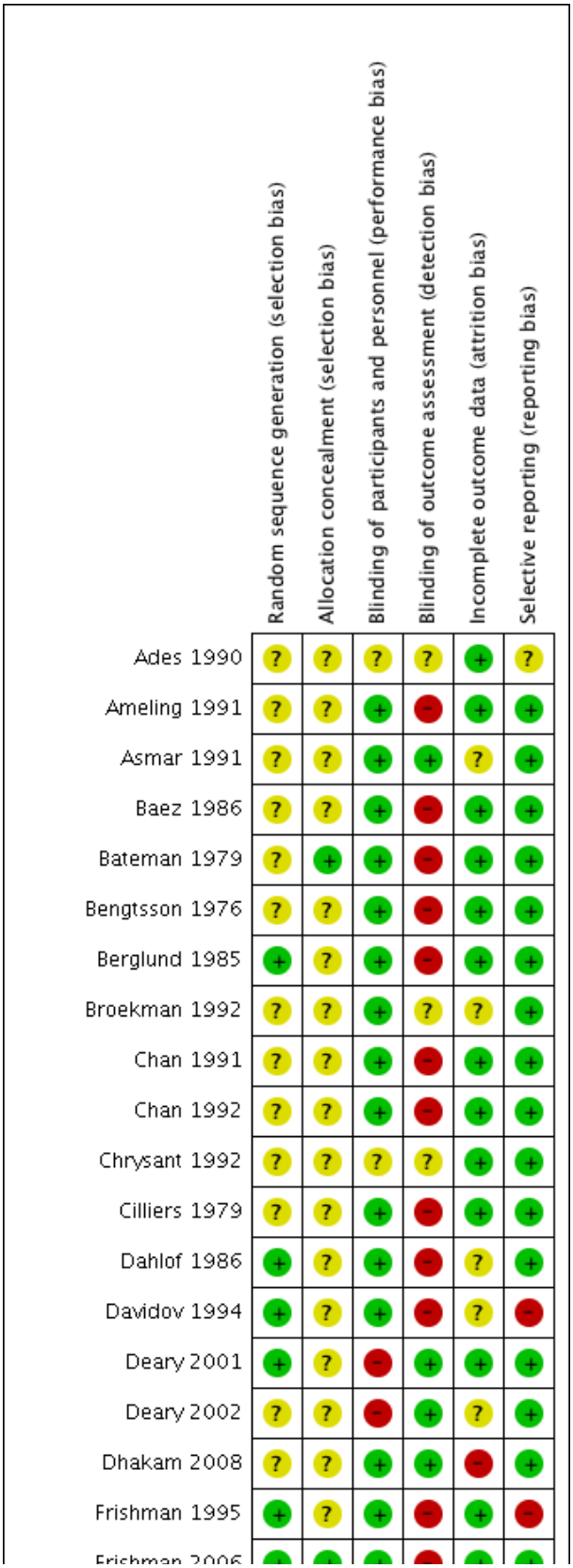


Figure 2. (Continued)

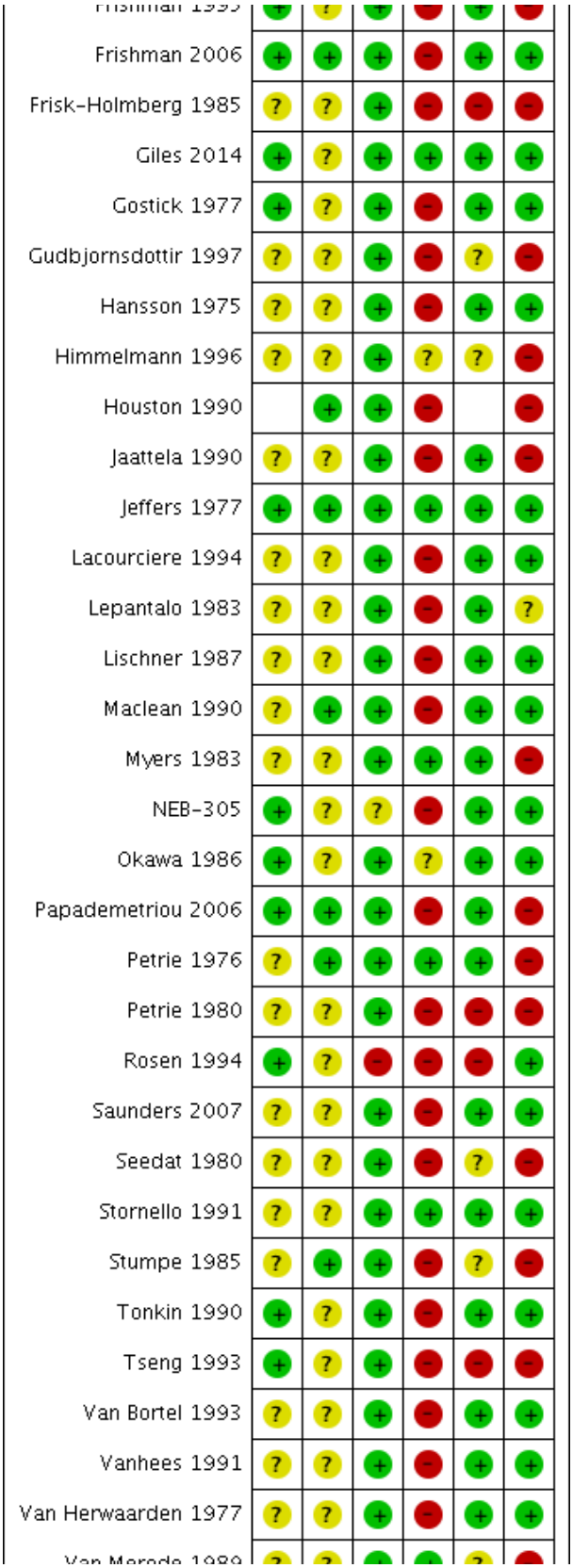
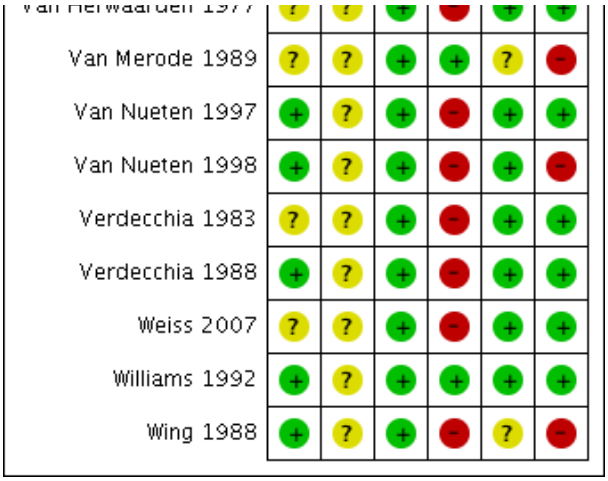


Figure 2. (Continued)



Allocation

Details regarding random sequence generation and allocation concealment were poorly reported in many of the included studies. This information was important in determining the potential of selection bias in this review. Because of poor reporting, it was difficult to judge the potential for selection bias. In the parallel studies, we examined the baseline characteristics of participants in each intervention group. We did not find any significant difference in baseline characteristics between the intervention groups which would raise concerns regarding selection bias. Hence, we did not find any evidence that suggested a high risk of selection bias in the parallel studies. It was impossible to assess whether randomisation was conducted properly in cross-over studies, thus there is an unclear risk of selection bias in cross-over trials.

Blinding

Beta blockers are well known for their ability to lower heart rate. The assessor could detect the difference in heart rate when measuring blood pressure. Using an automated machine to measure BP would mitigate this risk of detection bias. However this was not done in most of the included trials in this review. Therefore, the risk of detection and performance bias is high in this review.

Incomplete outcome data

Most of the studies reported the method by which they handled dropouts. The dropout rates were low and most of studies used an ITT analysis. Therefore, we judged that the risk of attrition bias in this review was low.

Selective reporting

All the studies included reported the SBP, DBP and heart rate as outcomes of the participants. Withdrawal due to adverse effects is an important outcome in clinical trials. Only two studies reported useful data on withdrawal due to adverse effects. The risk of reporting bias was high because most of the studies failed to report withdrawal due to adverse effects.

Other potential sources of bias

Funnel plots of the pooled data showed a paucity of small and less effective studies and positive outliers. The asymmetry of funnel plots indicated the high potential for publication bias (Sterne 2011). Some of the extreme outliers were large studies with a large effect that was questionable. It was not possible to prove that these trials were flawed, therefore we kept them in the review, however, they add to the suspicion of a high risk of bias. As a result, BP lowering estimates of the group combining the starting dose and twice the starting dose are likely to be overestimated.

Effects of interventions

See: **Summary of findings for the main comparison**

The primary outcomes and some key secondary outcomes are summarized in the Summary of findings for the main comparison.

The results below are presented in descending order according to the sample size.

Blood pressure lowering efficacy of nebivolol

Nebivolol is a beta-1 selective blocker which has been marketed in Canada since early 2013. Nebivolol is indicated for treatment of hypertension in Canada and the United States of America (USA) (eCPS; FDA). The recommended doses of nebivolol are 5 mg to 20 mg daily (eCPS). Twelve RCTs examining the blood pressure lowering efficacy of 1 mg to 40 mg per day nebivolol in 3209 hypertensive participants were included in this review. Eight of them were parallel studies and the other four were cross-over studies. In addition, NEB-305 was an unpublished RCT from an FDA report. The mean baseline BP of the participants in the included studies was 154.6/100.4 mmHg.

Please refer to Analysis 1.1, Analysis 1.2, Analysis 1.3 and Analysis 1.4 for the results of nebivolol. All nebivolol doses significantly lowered trough SBP and DBP compared to placebo. The test for subgroup differences by direct comparison included five large RCTs with multiple dosage subgroups. There was no dose-related effect within the recommended dose range (starting dose, twice the starting dose, four times the starting dose) for SBP (P = 0.47) and DBP (P = 0.52). The maximum BP lowering effect was seen at 5 mg/day (starting dose). Since there was no dose response within the recommended doses, we pooled the three dosages into subgroups (5 mg, 10 mg and 20 mg) to calculate the estimates for blood pressure lowering efficacy. The estimate for blood pressure lowering efficacy for nebivolol is -8/-6 mmHg. Heterogeneity was

significant in these subgroups and we discuss the validity of this estimate further in the Discussion.

Nebivolol 1.25 mg/day did not significantly lower heart rate. Starting from 2.5 mg/day, nebivolol significantly lowered heart rate compared to placebo. Heterogeneity in the 5 mg/day subgroup was significant. The test of subgroup differences by direct comparison was significant (P = 0.0004) for heart rate. Only nebivolol 5 mg/day significantly lowered pulse pressure. However, the 5 mg/day subgroup was also the only subgroup in which heterogeneity was significant.

Four RCTs, NEB-305; Saunders 2007; Van Nueten 1997; Weiss 2007, provided both peak and trough data in the same participants. We compared the difference in peak and trough effect for SBP and DBP. Peak measurements were not significantly different from trough measurements in SBP (Analysis 1.5). The BP lowering effect at peak was significantly greater than trough measurements for DBP, averaging 2 mmHg difference (Analysis 1.6).

The blood pressure variability was not significantly different between nebivolol and placebo for SBP (P = 0.61) and DBP (P = 0.52).

Blood pressure lowering efficacy of atenolol

Atenolol is indicated for the treatment of hypertension and angina in Canada and the USA (eCPS; FDA). The recommended doses for hypertension are 50 mg to 100 mg daily (FDA). Twenty-three RCTs examining the blood pressure lowering efficacy of 25 mg to 200 mg per day atenolol in 1119 hypertensive participants were included in this review. Seven of the included studies were parallel studies and the other 16 were cross-over studies. The mean baseline BP for the atenolol studies was 162.3/104.2 mmHg.

Please refer to Analysis 2.1, Analysis 2.2, Analysis 2.3 and Analysis 2.4 for the atenolol results. All atenolol doses significantly lowered SBP and DBP compared to placebo. The maximum BP lowering effect was shown at 100 mg/day (twice the starting dose). The test for subgroup differences within the recommended dose range (starting dose, twice the starting dose and four times the starting dose) by direct comparison was not significant for SBP (P = 0.56) and DBP (P = 0.22). However, only two small studies provided information for direct comparison. The test for subgroup differences by indirect comparison was not significant for SBP (P = 0.31) but significant for DBP (P = 0.04). Given this inconsistency, the evidence remains inconclusive that atenolol exhibits a dose-response effect.

We found significant heterogeneity in both 50 mg/day and 100 mg/day subgroups in SBP and DBP. We discuss the probable reasons for heterogeneity in the Discussion. These two subgroups contained the largest sample size. The estimate of blood pressure lowering efficacy combining the starting dose and twice the starting dose was -13/-11 mmHg.

Atenolol 25 mg/day did not significantly lower heart rate. Starting from 50 mg/day and higher, atenolol significantly lowered heart rate compared to placebo. The test for subgroup differences in the recommended dose range by direct comparison was significant for heart rate (P = 0.008).

Atenolol 50 mg/day and higher significantly lowered pulse pressure compared to placebo. There were no differences between 50 mg/day, 100 mg/day and 200 mg/day by direct comparison for pulse pressure.

Blood pressure variability was not significantly different between the treatment and placebo groups for SBP (P = 0.3) and DBP (P = 0.13).

Blood pressure lowering efficacy of metoprolol

Metoprolol is indicated for the treatment of hypertension, angina and stable acute myocardial infarction (MI) in Canada and the USA. The recommended doses for hypertension are 100 mg to 200 mg daily in Canada and 100 mg to 450 mg daily in the USA (eCPS; FDA). Nine RCTs examining the blood pressure lowering efficacy of 25 mg to 400 mg per day metoprolol in 1004 hypertensive participants were included in this review. Four of the included studies were parallel studies and the other five were cross-over studies. The mean baseline BP of the metoprolol studies was 154.4/100.3 mmHg.

Please refer to Analysis 3.1, Analysis 3.2, Analysis 3.3 and Analysis 3.4 for the metoprolol results. All metoprolol doses significantly lowered SBP and DBP compared to placebo. The maximum BP lowering effect was seen at 200 mg/day (twice the starting dose). The test for subgroup differences in the recommended dose range (100 mg/day to 400 mg/day) by direct comparison was not significant for both SBP (P = 0.12) and DBP (P = 0.12). Significant heterogeneity was present in the SBP 400 mg/day and DBP 200 mg/day subgroups. Since there was no definitive dose-response within the recommended range, we pooled all the recommended doses, 100 mg, 200 mg/day and 400 mg/day, to estimate the blood pressure lowering effects. The estimate of blood pressure lowering effect of metoprolol was -9/-8 mmHg.

Only five RCTs reported heart rate, therefore the sample size for heart rate was fairly small. However, all metoprolol doses significantly lowered heart rate compared to placebo. The test for subgroup differences by indirect comparison was significant in heart rate (P = 0.0007).

Metoprolol did not significantly change pulse pressure.

Metoprolol did not significantly change blood pressure variability compared to placebo for SBP (P = 0.56) or DBP (P = 0.86).

Blood pressure lowering efficacy of betaxolol

Please refer to the Analysis 5.1 to Analysis 5.4 for the results for betaxolol. Betaxolol is indicated for treatment of hypertension in the USA (FDA). The recommended daily doses of betaxolol are 10 mg/day to 20 mg/day. Two RCTs examined the BP lowering efficacy of betaxolol at dosage of 5 mg/day to 20 mg/day in hypertensive 627 participants were included in this review. The duration of both studies was four weeks. Ameling 1991 was a cross-over study and Williams 1992 was a parallel study. Both studies measured BP using a mercury sphygmomanometer. Williams 1992 reported that they measured BP 24 hours after the last dose (trough). Ameling 1991 did not report the time of the measurement. The mean baseline BP of the included studies was 158.9/102.8 mmHg.

All doses of betaxolol significantly lowered SBP, DBP and heart rate. Williams 1992 provided data for direct comparison between the dose subgroup. There was no significant difference in BP lowering effect between the dose subgroups. Since there was no significant

difference between the dosages, we pooled all three doses to estimate the mean effect. The estimated BP lowering effect of betaxolol is -11/-8 mmHg.

Only 20 mg/day betaxolol also significantly lowered pulse pressure.

We were not able to perform analysis on BP variability because neither of the two included studies reported SD.

Blood pressure lowering efficacy of bisoprolol

Bisoprolol is indicated for the treatment of hypertension in Canada and the USA. The recommended doses for hypertension are 5 mg to 20 mg/day in Canada and the USA (eCPS; FDA). Seven RCTs examining the blood pressure lowering efficacy of 5 mg to 20 mg/day bisoprolol in 622 people with hypertension were included in this review. Three of the included studies were parallel design and the other four were cross-over design. The mean baseline BP was 151.2/100.1 mmHg.

Please refer to Analysis 4.1, Analysis 4.2, Analysis 4.3 and Analysis 4.4 for the results of bisoprolol. All doses of bisoprolol significantly lowered SBP and DBP compared to placebo. There was significant heterogeneity for 5 mg/day (starting dose) subgroup for both outcomes. The test for subgroup differences in the recommended dose range by direct comparison was not significant in SBP (P = 0.76) and DBP (P = 0.32). Since there was no significant difference between the subgroups, we combined the three subgroups to obtain the estimate of BP lowering of bisoprolol, -10/-8 mmHg.

All doses of bisoprolol significantly lowered heart rate compared to placebo. The test for subgroup differences by direct comparison was not significant in heart rate (P = 0.12).

Only 5 mg/day (starting dose) bisoprolol significantly lowered pulse pressure. This effect was not seen in other subgroups.

There was no significant difference in blood pressure variability between treatment and placebo for SBP (P = 0.66) or DBP (P = 0.96).

Blood pressure lowering efficacy of bevantolol

Please refer to Analysis 6.1, Analysis 6.2, Analysis 6.3, and Analysis 6.4 for the results for bevantolol. Bevantolol is not available in Canada, the USA or the European Union (EU). We did not find the product monograph or recommended starting dose for bevantolol from these government agencies. We included one parallel study (Okawa 1986) examining the BP lowering efficacy of 100 mg/day to 400 mg/day bevantolol in 139 hypertensive patients for six weeks in this review.

Bevantolol did not significantly lower SBP, DBP, heart rate or pulse pressure compared to placebo. Bevantolol did not significantly change BP variability. The end treatment SD for SBP was 20.8 for the bevantolol group and 19.8 for the placebo group. The end treatment SD for DBP was 13.1 for the bevantolol group and 12.6 for the placebo group.

Blood pressure lowering efficacy of pafenolol

Please refer to Analysis 7.1, Analysis 7.2, Analysis 7.3 and Analysis 7.4 for the results of pafenolol. Pafenolol is not available in Canada, the USA or the EU. We did not find the product monograph or recommended starting dose for pafenolol on the websites of these government agencies. Two RCTs examining the blood pressure lowering efficacy of 25 mg/day to 100 mg/day pafenolol in 161 hypertensive participants were included. Both studies were parallel studies with treatment periods of four weeks. The mean baseline BP was 161.1/109.6 mmHg.

Pafenolol did not significantly lower SBP, DBP or pulse pressure. Pafenolol 50 mg/day and 100 mg/day significantly lowered heart rate.

Blood pressure lowering efficacy of practolol

Please refer to Analysis 8.1, Analysis 8.2, Analysis 8.3 and Analysis 8.4 for the results of practolol. Practolol is not available in Canada, the USA or the E.U. We did not find the product monograph or recommended starting dose for practolol on the websites of these government agencies. We included one cross-over study examining the blood pressure lowering effect of 600 mg/day practolol in 24 hypertensive participants for four weeks in this review. The baseline BP was 182.9/123.3 mmHg.

Practolol 600 mg/day significantly lowered SBP, DBP, heart rate and pulse pressure compared to placebo.

Pooled haemodynamic effect of beta-1 selective blockers

We pooled the data for all available beta-1 selective blockers, based on the recommended starting doses. This allowed us to estimate the blood pressure lowering effect of beta-1 selective blockers as a whole subclass, as well as to compare it to other classes of antihypertensive drugs. Please refer to Analysis 9.1, Analysis 9.2, Analysis 9.3 and Analysis 9.4 for the results of beta-1 blockers.

All pooled beta-1 blocker doses significantly lowered SBP and DBP compared to placebo. The starting dose and twice the starting dose subgroups each contained over 2000 participants, which provided good estimates to represent this subclass of beta blockers. Heterogeneity was significant in these two subgroups. The source of heterogeneity is explored in the Discussion. The test for subgroup differences in the starting dose, twice the starting dose, four times the starting dose and eight times the starting dose subgroups by direct comparison was not significant for SBP (P = 0.23) and DBP (P = 0.11). The BP lowering estimate (SBP/DBP) combining the starting dose and twice the starting dose subgroups was -10/-8 mmHg.

All doses of beta-1 blockers significantly lowered heart rate. Beta-1 selective blockers significantly lowered pulse pressure at the starting dose, twice the starting dose and four times the starting dose compared to placebo. The test for subgroup differences by direct comparison in pulse pressure was not significant.

Blood pressure variability

We tested the overall effect of beta-1 blockers on BP variability using an unpaired t-test. We extracted end treatment SD from parallel studies for the beta-1 blocker group and the placebo group. Beta-1 blockers did not significantly change BP variability in SBP (P = 0.83) or DBP (P = 0.52). The overall mean of end treatment SD for beta-1 blockers (SBP/DBP) was 14.5/8.6 and placebo group was 14.9/8.5.

Withdrawal due to adverse effects

We pooled the data for withdrawal due to adverse effects (Analysis 9.5). Out of the 56 RCTs, only three RCTs reported withdrawal due

to adverse effects data that could be used for the analysis. In these three RCTs, there was no significant difference in withdrawal due to adverse effects between treatment and placebo (RR 0.85 [0.50, 1.45]).

DISCUSSION

Summary of main results

Nebivolol

The maximum blood pressure lowering effect of nebivolol occurred at 5 mg/day. Doses higher than 5 mg/day did not provide additional BP lowering effects. The data from 5 mg/day, 10 mg/day and 20 mg/day (starting dose, twice the starting dose and four times the starting dose) were pooled to estimate the average BP lowering effect of nebivolol, which was -8/-6 mmHg. The funnel plots for nebivolol showed a paucity of small negative studies (Figure 3; Figure 4). This suggested that small negative studies were not published. The estimate above was likely an over estimation of the true effect. The funnel plots also showed several outliers on the left hand side of the graph. These positive outliers would exaggerate the effect.

Figure 3. Funnel plot of nebivolol 5 mg to 20 mg (SBP)

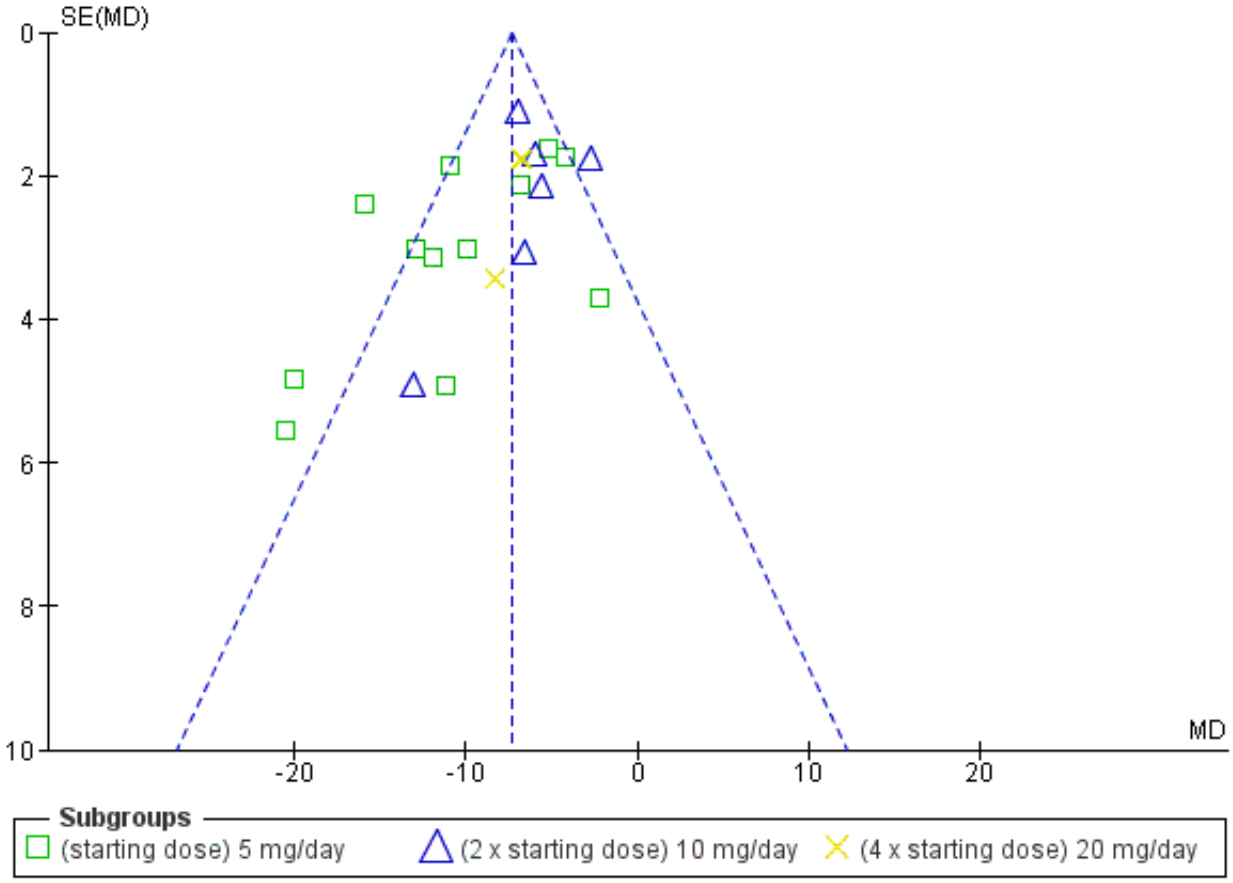
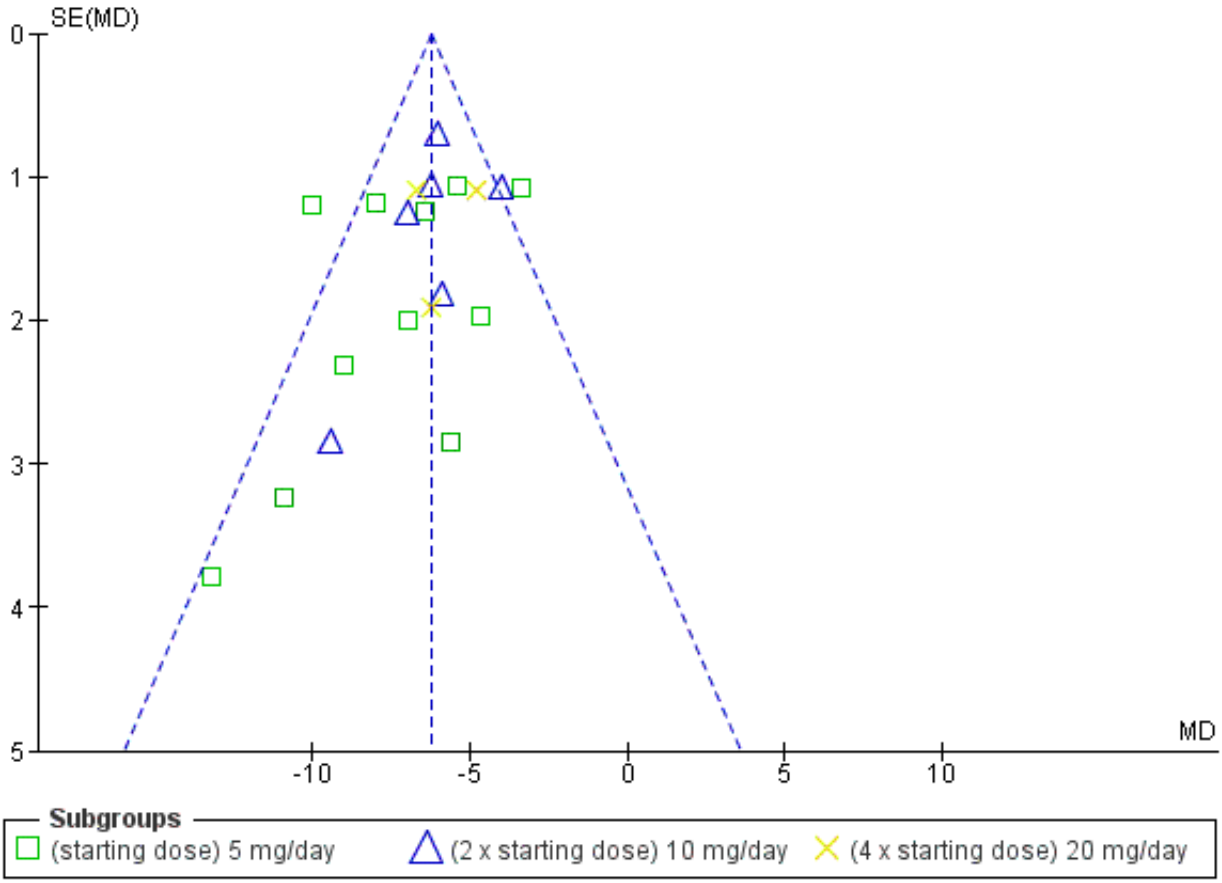


Figure 4. Funnel plot of nebivolol 5 mg to 20 mg (DBP)



Nebivolol lowered systolic and diastolic BP to a similar degree, and therefore it had only a small effect on pulse pressure. Heterogeneity in the 5 mg/day subgroup suggested that the statistically significant effect on pulse pressure could be caused by variation, as no other dose of nebivolol showed a similar effect.

Peak to trough difference

Only four nebivolol studies reported both peak and trough measurements. If there was a greater effect at peak (seen with some diastolic BP measurements) the effect was small (2 mmHg).

Atenolol

Both the recommended starting dose (50 mg daily) subgroup and twice the starting dose (100 mg daily) subgroup contained a large number of subjects and provided a good estimate of the blood pressure lowering efficacy of atenolol. Funnel plots were used to identify extreme outliers and assessment of bias. The funnel plots of the starting dose did not show any extreme outliers or provide evidence of asymmetry which would suggest publication bias.

In the twice the starting dose subgroup, the funnel plot identified Lischner 1987 as an extreme outlier for both SBP and DBP. Another RCT (Ravid 1985) from the same laboratory was also identified as an extreme outlier in the Cochrane review on non-selective beta blockers (Wong 2014a). These data are therefore of questionable validity. This represented a common problem in performing the systematic review and meta-analysis, as such studies lead to an overestimation of the magnitude of blood pressure lowering effect. If we removed the extreme outlier, the estimate of twice the starting dose decreased from -15/-13 mmHg to -12/-10 mmHg. Removing it would also decrease the overall estimate of the pooled atenolol starting dose and twice the starting dose subgroups from -13/-11 mmHg to -11/-9 mmHg, which was closer to the overall estimates of the class.

Atenolol was the only beta-1 blocker that significantly lowered pulse pressure across several doses. The combined estimate of the pulse pressure effect of starting dose, twice and four times the starting dose atenolol was small (-2 mmHg [1-3]). It did not show a dose-response effect and is unlikely to be clinically significant.

Metoprolol

Most of the data for metoprolol came from two studies which tested the dose-response effect of the drug at several doses (Frishman 2006, Papademetriou 2006). These two RCTs showed a greater BP lowering in the recommended dose range compared to lower doses (25 mg/day and 50 mg/day). However, the different doses within the recommended dose range did not show a significant dose response effect. The mean BP lowering effect of the 100 mg/day, 200 mg/day and 400 mg/day (starting dose, twice and four times the starting dose) was -9/-8 mmHg.

Bisoprolol

No additional BP lowering effect was seen for doses higher than the recommended starting dose of bisoprolol. The mean BP lowering effect of the 5 mg/day, 10 mg/day and 20 mg/day (starting dose, twice the starting dose and four times the starting dose) was -11/-8 mmHg. This was likely to be exaggerated because of the presence of two extreme positive outliers (Deary 2001, Deary 2002) in the data.

Betaxolol, bevantolol, pafenolol and practolol

The sample sizes of these four beta-1 blockers were small. They contributed little weight to the overall pooled estimates. Their estimates are reported in the Main results.

Overall pooled blood pressure lowering effect of beta-1 blockers

The sample size for the beta-1 selective blockers was the largest of the four subclasses of beta blockers. The pooled data included 6313 participants from 51 RCTs and multiple dosages. The data set provided the best opportunity to explore whether there was a graded dose-response effect. The findings showed a similar and smaller BP lowering effect at a quarter of the starting dose and half the starting dose, but then a flat and similar BP lowering for the starting dose, twice, four times and eight times the starting dose (see Analysis 9.1; Analysis 9.2.). Twice the starting dose subgroups had the most data and exhibited considerable heterogeneity, which we explore below. The lack of a dose-response effect above twice the starting dose suggests that higher doses of beta-1 blockers were not more effective in lowering BP.

In Analysis 9.10 and Analysis 9.11, we demonstrated that the primary source of heterogeneity in the twice the starting dose subgroup was the difference in BP lowering effect between the individual beta-1 blockers. Atenolol showed the largest effect size among the five beta-1 blockers. In the discussion for atenolol, we explained that the estimate of the twice the starting dose subgroup of atenolol could be exaggerated due to an extreme outlier. The effect size of this atenolol subgroup would change from -15/-13 mmHg to -12/-10 mmHg if we removed the extreme outlier from the analysis. We also considered the fact that mean baseline BP of atenolol studies (162/104 mmHg) was higher than the other beta-1 blockers. In addition, most studies for atenolol, metoprolol and betaxolol measured BP at peak hours. Peak measurements would also contribute to a greater effect size.

Difference in pharmacodynamic properties could also have contributed to the difference in BP lowering efficacy. Heart rate reduction during exercise was used for many beta-1 blockers to test the potency of beta-1 blockade. Bisoprolol 10 mg (at twice the starting dose) had equivalent exercise heart rate percentage change from baseline compared to 50 mg atenolol (starting dose) and 100 mg metoprolol (starting dose) (Lancaster 1988). Five mg nebivolol (starting dose) had an equivalent effect compared to 100 mg atenolol (twice the starting dose) (Veverka 2006). If beta-1 blockade was the dominant mechanism by which blood pressure was lowered by beta blockers, nebivolol should have lowered BP the most and bisoprolol the least. As this did not fit with the data, potency of beta-1 blocking ability did not explain the difference in blood pressure lowering effect.

Beta-1 selectivity also might explain the differences. Both nebivolol and bisoprolol are highly beta-1 selective. The beta-1/beta-2 selectivity ratios were 321 fold for nebivolol and 100 fold for bisoprolol (Lancaster 1988; Veverka 2006). The selectivity ratios for atenolol, metoprolol and betaxolol were much less, at 35 fold, 40 fold and 20 fold respectively (Lancaster 1988). In this case, it appeared that beta blockers with less beta-1 selectivity lower BP by a greater magnitude.

The mechanism by which beta blockers lower blood pressure is the most likely explanation for differences in BP lowering effect. However, studying the pharmacodynamic properties of beta blockers is notoriously difficult. The methods to test pharmacodynamic properties vary between research groups. The outcomes are often not comparable to each other (Fitzgerald 1991). It is thus difficult to fully explain the observed differences in BP lowering effect between different beta-1 blockers.

The starting dose and twice the starting dose subgroups contained the largest sample size. The best estimate of BP lowering efficacy for beta-1 blockers was determined by combining the results from all the starting dose and twice the starting doses. It was -10/-8 mmHg.

Pulse pressure

Atenolol was the only beta-1 blocker that consistently lowered pulse pressure at different doses. This effect was also seen in the pooled analysis. Since no other beta-1 blocker exhibited a similar effect on pulse pressure it is more likely that the atenolol data are incorrect.

Overall completeness and applicability of evidence

This review provides the most up-to-date assessment of the blood pressure lowering efficacy of beta-1 selective blockers. All the studies included had the same primary objective which was to compare the blood pressure effect of beta-1 blockers and placebo. This review contains a fairly large sample size for the continuous outcomes that we examined.

Quality of the evidence

Summary of findings for the main comparison summarises the important findings based on combining the data from the starting dose and twice the starting dose of beta-1 selective blockers, and incorporates the quality of evidence in this review.

We have included 56 RCTs examining the BP lowering efficacy of eight beta-1 blockers in 7812 people with hypertension in this review. The large sample size provided adequate power to draw robust conclusions. The risk of detection bias was of concern in beta blocker studies. Most of the included studies did not use automated machines when measuring BP, which would be the best way to mitigate the risk of detection bias. Therefore, the risk of detection bias by loss of blinding was high. Nebivolol and atenolol contributed a large portion of data to our pooled analyses. Both of the beta-1 blockers showed high risk of publication bias either due to skewed funnel plots or the presence of extreme outliers.

Pulse pressure data was seldom reported in the trials. We calculated pulse pressure by subtracting the reduction in DBP from the reduction in SBP. Indirectness of this outcome was the reason the evidence was further downgraded for pulse pressure. For these reasons, the quality of evidence was judged to be low to very low in the 'Summary of findings' table.

Potential biases in the review process

The rigid methodology and comprehensive search strategy minimised the potential for bias in selection of included studies. The search of citations in the three databases was performed by the Cochrane Hypertension Information Specialist. Once we had the set of citations, we sorted through them following the inclusion criteria. This process minimised any grey areas that may have introduced bias.

On the occasions that data had to be obtained from figures, two reviewers extracted data independently and then the average of the two values was used. This minimised the potential of human error during the data extraction process. We are confident that the potential for bias during the review process was low.

Agreements and disagreements with other studies or reviews

Two published reviews (Chen 2010; Law 2005) reported the blood pressure lowering efficacy of beta blockers. Chen 2010 examined the additional effect of beta blockers in combination with other antihypertensive drugs. Law 2005 examined the BP lowering effect of antihypertensive drugs, including beta-blockers, as monotherapy. Both reviews pooled all the subclasses of beta blockers and doses together, assuming that they had similar effects. We were able to show that beta-1 selective blockers could have significantly different BP lowering effects from the other sub-classes of beta blockers. Our review is unique in the sense that we did not assume that all beta blockers lowered blood pressure similarly.

When compared to the other subclasses, beta-1 selective blockers appeared to lower BP more than dual receptor blockers (Wong 2015) and partial agonists (Wong 2014b). Nonselective beta blockers and beta-1 selective blockers appeared to lower blood pressure similarly (Wong 2014a), however most trials included in the nonselective beta blocker review measured BP at peak effect. These are indirect comparisons, but represent fairly strong evidence that the BP lowering efficacy of different subclasses of beta blockers are not the same. Direct head-to-head RCTs would be the best way to determine whether the differences between the subclasses is real.

There are a number of reasons why the pooled estimate of BP lowering for beta-1 selective beta blockers (-10/8 mmHg) is greater than the real effect. One of these reasons is that about half of the trials measured the effect at peak rather than trough. The estimate of BP lowering at trough (-8/-7 mmHg) is less than the overall pooled estimate and is the number that is best compared to other drug classes.

Other Cochrane reviews have compared antihypertensive drug classes with placebo and used similar inclusion/exclusion criteria to this review. Based on indirect comparison, the pooled trough SBP lowering effect of beta-1 selective blockers (-8 mmHg) is similar to the average SBP reduction for thiazide diuretics (-9 mmHg) (Musini 2014), angiotensin converting enzyme (ACE) inhibitors (-8 mmHg) (Heran 2008a), angiotension receptor blockers (ARBs) (-9 mmHg) (Heran 2008b) and renin inhibitors (-8 mmHg) (Musini 2008). In contrast the trough DBP lowering of beta-1 selective blockers (-7 mmHg) is greater than that for thiazide diuretics (-4 mmHg) (Musini 2014), ACE inhibitors (-5 mmHg) (Heran 2008a), ARBs (-5 mmHg) (Heran 2008b) and renin inhibitors (-5 mmHg) (Musini 2008). This provides fairly strong evidence that the BP lowering effect of different classes of drugs is not the same as has been assumed by others (Law 2005).

The property of beta-blockers to lower DBP to a similar extent to SBP explains the fact that beta-1 selective blockers have no effect on pulse pressure. This finding is similar to the other beta blocker subclasses and is substantially less than the average reduction of pulse pressure seen with thiazides (-5 mmHg) (Musini 2014) and drugs that inhibit renin angiotensin system (-3 mmHg) (Heran 2008a; Heran 2008b; Musini 2008). This finding is important and might be the explanation as to why first-line beta blockers (Wiysonge 2012) do not reduce mortality and morbidity as much as first-line thiazides; 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 low quality evidence that in people with mild to moderate hypertension, beta-1 selective blockers lowered BP by an average of -10/-8 mmHg and reduced heart rate by 11 beats per minute as compared to placebo. The effect of beta-1 blockers at peak hours, -12/-9 mmHg, was greater than the reduction at trough hours, -8/-7 mmHg. Beta-1 blockers lowered BP maximally at twice the recommended starting doses. Individual beta-1 blockers did not exhibit a significant graded dose-response effect on SBP and DBP over the recommended dose range. This suggests that higher doses of beta-1 blockers might not provide additional BP lowering effects, however might cause more side effects.

A graded dose-response of beta-1 blockers on heart rate was evident. Higher dose beta-1 blockers lowered heart rate to a greater amount when compared to lower doses. Beta-1 selective beta blockers did not reduce pulse pressure with the exception of atenolol, which reduced it by 2 mmHg.

Implications for research

1. Better reporting of method of randomisation and allocation concealment in future RCTs is required.
2. Beta blocker studies should use automated machines to measure blood pressure in order to minimise detection bias.
3. All RCTs measuring blood pressure lowering effects must be published.
4. Future blood pressure lowering trials must report: resting blood pressure and heart rate measured in a standard sitting position; the time after administration of the drug that the BP was measured; the standard deviation or standard error of mean of all measurements; and withdrawals due to adverse effects in the treatment and placebo arms.
5. Future systematic reviews should focus on comparing the BP lowering effects of different beta blockers and sub-classes of beta blockers in head-to-head trials using automated BP measurements.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the help provided by the Cochrane Hypertension Group. We would like to thank Stephen Adams for retrieving the articles.

REFERENCES

References to studies included in this review

Ades 1990 *{published data only}*

Ades PA, Gunther PG, Meyer WL, Gibson TC, Maddalena J, Orfeo T, et al. Cardiac and skeletal muscle adaptations to training in systemic hypertension and effect of beta blockade (metoprolol or propranolol). *American Journal of Cardiology* 1990;**66**(5):591-6.

Ameling 1991 *{published data only}*

* Ameling EH, de Korte DF, Man in 't Veld A. Impact of diagnosis and treatment of hypertension on quality of life: a double-blind, randomized, placebo-controlled, cross-over study of betaxolol. *Journal of Cardiovascular Pharmacology* 1991;**18**(5):752-60.

Asmar 1991 *{published data only}*

Asmar RG, Kerihuel JC, Girerd XJ, Safar ME. Effect of bisoprolol on blood pressure and arterial hemodynamics in systemic hypertension. *American Journal of Cardiology* 1991;**68**(1):61-4.

Baez 1986 *{published data only}*

Baez MA, Garg DC, Jallad NS, Weidler DJ. Antihypertensive effect of doxazosin in hypertensive patients: comparison with atenolol. *British Journal of Clinical Pharmacology* 1986;**21**(Suppl 1):63s-67s. [PUBMED: 2939869]

Bateman 1979 *{published data only}*

Bateman DN, Dean CR, Mucklow JC, Bulpitt CJ, Dollery CT. Atenolol and chlorthalidone in combination for hypertension. *British Journal of Clinical Pharmacology* 1979;**7**(4):357-63.

Bengtsson 1976 *{published data only}*

Bengtsson C. The effect of metoprolol - a new selective adrenergic beta1-receptor blocking agent-- in mild hypertension. *Acta Medica Scandinavica* 1976;**199**(1-2):65-70.

Berglund 1985 *{published data only}*

Berglund G, de Faire U, Castenfors J, Andersson G, Hartford M, Liedholm H, et al. Monitoring 24-hour blood pressure in a drug trial. Evaluation of a noninvasive device. *Hypertension* 1985;**7**:688-94.

Broekman 1992 *{published data only}*

Broekman CP, Haensel SM, Van de Ven LLM, Slob AK. Bisoprolol and hypertension: effects on sexual functioning in men. *Journal of Sex & Marital Therapy* 1992;**18**(4):325-31.

Chan 1991 *{published data only}*

Chan TYK, Woo KS, Critchley JAJH, Swaminathan R, Nicholls MG. Effects of nebivolol on blood pressure, hormones and cardiac function in Chinese subjects with essential hypertension. *Drug investigations* 1991;**3**:98-104.

Chan 1992 *{published data only}*

Chan TY, Woo KS, Nicholls MG. The application of nebivolol in essential hypertension: a double-blind, randomized, placebo-controlled study. *International Journal of Cardiology* 1992;**35**(3):387-95.

Chrysant 1992 *{published data only}*

Chrysant SG, Chappel C, Farnham DJ, Levin B, Lueg M, McCluskey D, et al. Antihypertensive and metabolic effects of single and combined atenolol regimens. *Journal of Clinical Pharmacology* 1992;**32**(1):61-5.

Cilliers 1979 *{published data only}*

Cilliers AJ. Atenolol as primary therapy in previously untreated hypertensives and as an adjuvant to other therapy. A South African multicentre study. *South African Medical Journal* 1979;**Suid-Afrikaanse Tydskrif Vir Geneeskunde. 55**(9):321-4.

Dahlof 1986 *{published data only}*

Dahlof B, Sjoberg KH, Flygt C, Jern S, Hansen S, Hansson L, et al. Pafenolol in hypertension: a double-blind randomized trial of a new beta 1-selective adrenoceptor blocker. *Journal of Cardiovascular Pharmacology* 1986;**8**(1):55-9.

Davidov 1994 *{published data only}*

Davidov ME, Singh SP, Vlachakis ND, Blumenthal JB, Simon JS, Bryzinski BS, et al. Bisoprolol, a once-a-day beta-blocking agent for patients with mild to moderate hypertension. *Clinical Cardiology* 1994;**17**(5):263-8.

Deary 2001 *{published data only}*

Deary AJ, Schumann AL, Murfet H, Haydock SF, Foo RSY, Brown MJ. Double-blind, placebo-controlled crossover comparison of five classes of antihypertensive drugs. *Journal of Hypertension* 2002;**20**:771-7.

Deary 2002 *{published data only}*

Deary AJ, Schumann AL, Murfet H, Haydock S, Foo RS, Brown MJ. Influence of drugs and gender on the arterial pulse wave and natriuretic peptide secretion in untreated patients with essential hypertension.[see comment]. *Clinical Science* 2002;**103**(5):493-9.

Dhakam 2008 *{published data only}*

Dhakam Z, Yasmin, McEniery CM, Burton T, Brown MJ, Wilkinson IB. A comparison of atenolol and nebivolol in isolated systolic hypertension. *Journal of Hypertension* 2008;**26**:351-6.

Frishman 1995 *{published data only}*

Frishman WH, Burris JF, Mroczek WJ, Weir MR, Alemayehu D, Simon JS, et al. First-line therapy option with low-dose bisoprolol fumarate and low-dose hydrochlorothiazide in patients with stage I and stage II systemic hypertension. *Journal of Clinical Pharmacology* 1995;**35**(2):182-8.

Frishman 2006 *{published data only}*

Frishman WH, Hainer JW, Sugg J, M-FACT Study Group. A factorial study of combination hypertension treatment with metoprolol succinate extended release and felodipine extended release results of the Metoprolol Succinate-Felodipine Antihypertension Combination Trial (M-FACT). *American Journal of Hypertension* 2006;**19**(4):388-95.

Frisk-Holmberg 1985 *{published data only}*

Frisk-Holmberg M, Juhlin-Dannfelt A, Astrom H. Haemodynamic and metabolic responses to prolonged exercise after chronic beta 1-adrenoceptor blockade in hypertensive man. *Clinical Physiology* 1985;**5**(3):231-42.

Giles 2014 *{published data only}*

Giles TD, Weber MA, Basile J, et al. Efficacy and safety of nebivolol and valsartan as fixed-dose combination in hypertension: a randomised, multicentre study. *Lancet* 2014;**383**:1889-98.

Gostick 1977 *{published data only}*

Gostick NK, Mayhew SR, Million R, Sagar D, Suxena SR, Ingram DF, et al. A dose-response study of atenolol in mild to moderate hypertension in general practice. *Current Medical Research & Opinion* 1977;**5**(2):179-84.

Gudbjornsdottir 1997 *{published data only}*

Gudbjornsdottir S, Fowelin J, Elam M, Attvall S, Bengtsson BA, Marin P, et al. The effect of metoprolol treatment on insulin sensitivity and diurnal plasma hormone levels in hypertensive subjects. *European Journal of Clinical Investigation* 1997;**27**(1):29-35.

Hansson 1975 *{published data only}*

Hansson L, Aberg H, Karlberg BE, Westerlund A. Controlled study of atenolol in treatment of hypertension. *British Medical Journal* 1975;**2**(5967):367-70.

Himmelmann 1996 *{published data only}*

Himmelmann A, Hedner T, Snoeck E, Lundgren B, Hedner J. Haemodynamic effects and pharmacokinetics of oral d- and l-nebivolol in hypertensive patients. *European Journal of Clinical Pharmacology* 1996;**51**(3-4):259-64.

Houston 1990 *{published data only}*

Houston MC, Burger C, Hays JT, Nadeau J, Swift L, Bradley CA, et al. The effects of clonidine hydrochloride versus atenolol monotherapy on serum lipids, lipid subfractions, and apolipoproteins in mild hypertension. *American Heart Journal* 1990;**120**(1):172-9.

Jaattela 1990 *{published data only}*

Jaattela A, Baandrup S, Houtzagers J, Westergren G. The efficacy of low dose metoprolol CR/ZOK in mild hypertension and in elderly patients with mild to moderate hypertension. *Journal of Clinical Pharmacology* 1990;**30**(2 Suppl):S66-71.

Jeffers 1977 *{published data only}*

Jeffers TA, Webster J, Petrie JC, Barker NP. Atenolol once-daily in hypertension. *British Journal of Clinical Pharmacology* 1977;**4**(5):523-7.

Lacourciere 1994 *{published data only}*

Lacourciere Y, Arnott W. Placebo-controlled comparison of the effects of nebivolol and low-dose hydrochlorothiazide as monotherapies and in combination on blood pressure and lipid profile in hypertensive patients. *Journal of Human Hypertension* 1994;**8**(4):283-8.

Lepantalo 1983 *{published data only}*

* Lepantalo M, Totterman KJ. Effect of long-term beta-adrenergic-blockade on calf blood flow in hypertensive patients. *Clinical Physiology* 1983;**3**(1):35-42.

Lepantalo MJ, Totterman KJ. Lower limb haemodynamics during antihypertensive treatment with metoprolol and propranolol. *International Angiology* 1985;**4**(2):225-8.

Lischner 1987 *{published data only}*

Lischner M, Lang R, Jutrin I, Ravid M. Atenolol vs. amiloride-hydrochlorothiazide in the treatment of mild to moderate hypertension: a double-blind, crossover, placebo-controlled study. *Drug Intelligence & Clinical Pharmacy* 1987;**21**(1 Pt 1):43-6.

Maclean 1990 *{published data only}*

Maclean D, Mitchell ET, Lewis R, Irvine N, McLay JS, McEwen J, et al. Comparison of once daily atenolol, nitrendipine and their combination in mild to moderate essential hypertension. *British Journal of Clinical Pharmacology* 1990;**29**(4):455-63.

Myers 1983 *{published data only}*

Myers MG, de Champlain J. Effects of atenolol and hydrochlorothiazide on blood pressure and plasma catecholamines in essential hypertension. *Hypertension* 1983;**5**(4):591-6.

NEB-305 *{unpublished data only}*

Mylan Bertek Pharmaceuticals. A study of the safety and efficacy of nebivolol in hypertensive patients. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021742s000TOC.cfm (accessed Oct 2011).

Okawa 1986 *{published data only}*

Okawa KK. Dose response studies of bevantolol in hypertensive patients. *Angiology* 1986;**37**:233-8.

Papademetriou 2006 *{published data only}*

Papademetriou V, Hainer JW, Sugg J, Munzer D, ATTACH Study Group. Factorial antihypertensive study of an extended-release metoprolol and hydrochlorothiazide combination. *American Journal of Hypertension* 2006;**19**(12):1217-25.

Petrie 1976 *{published data only}*

Petrie JC, Galloway DB, Jeffers TA, Millar HR, Smith MC, Wood RA, et al. Methyldopa and propranolol or practolol in moderate hypertension. *British Medical Journal* 1976;**2**(6028):137-9.

Petrie 1980 *{published data only}*

Petrie JC, Jeffers TA, Robb OJ, Scott AK, Webster J. Atenolol, sustained-release oxprenolol, and long-acting propranolol in hypertension. *British Medical Journal* 1980;**280**(6231):1573-4.

Rosen 1994 *{published data only}*

Rosen RC, Kostis JB, Jekelis A, Taska LS. Sexual sequelae of antihypertensive drugs: treatment effects on self-report and physiological measures in middle-aged male hypertensives. *Archives of Sexual Behavior* 1994;**23**(2):135-52.

Saunders 2007 *{published data only}*

Saunders E, Smith WB, DeSalvo KB, Sullivan WA. The efficacy and tolerability of nebivolol in hypertensive African American patients. *Journal of Clinical Hypertension* 2007;**9**(11):866-75.

Seedat 1980 *{published data only}*

Seedat YK. Trial of atenolol and chlorthalidone for hypertension in black South Africans. *British Medical Journal* 1980;**281**(6250):1241-3.

Stornello 1991 *{published data only}*

Stornello M, Valvo EV, Scapellato L. Comparative effects of enalapril, atenolol and chlorthalidone on blood pressure and kidney function of diabetic patients affected by arterial hypertension and persistent proteinuria. *Nephron* 1991;**58**(1):52-7.

Stumpe 1985 *{published data only}*

Stumpe K, Kolloch R, Mathieu M, Capone P. A comparison of celiprolol and atenolol in the treatment of hypertension: a placebo controlled double blind study. *British Journal of Clinical Practice* 1985;**Supplement. 40**:73-5.

Tonkin 1990 *{published data only}*

Tonkin AL, Wing LM, Russell AE, West MJ, Bune AJ, Morris MJ, et al. Diltiazem and atenolol in essential hypertension: additivity of effects on blood pressure and cardiac conduction with combination therapy. *Journal of Hypertension* 1990;**8**(11):1015-9.

Tseng 1993 *{published data only}*

Tseng C-D, Chiang F-T, Hsu K-L, Tseng Y-Z, Hu W-H, Chen J-S, et al. Short-term efficacy and safety of bisoprolol in treatment of patients with mild-to-moderate essential hypertension - a two-center, double-blind study in Taiwan. *Acta Cardiologica Sinica* 1993;**9**(3):155-60.

Van Bortel 1993 *{published data only}*

Van Bortel LM, Breed JG, Joosten J, Kragten JA, Lustermans FA, Mooij JM, et al. Nebivolol in hypertension: a double-blind placebo-controlled multicenter study assessing its antihypertensive efficacy and impact on quality of life. *Journal of Cardiovascular Pharmacology* 1993;**21**(6):856-62.

Vanhees 1991 *{published data only}*

Vanhees L, Fagard R, Lijnen P, Amery A. Effect of antihypertensive medication on endurance exercise capacity in hypertensive sportsmen. *Journal of Hypertension* 1991;**9**(11):1063-8.

Van Herwaarden 1977 *{published data only}*

Van Herwaarden CL, Fennis JF, Binkhorst RA, Van't Laar A. Haemodynamic effects of adrenaline during treatment of hypertensive patients with propranolol and metoprolol. *European Journal of Clinical Pharmacology* 1977;**12**(6):397-402.

Van Merode 1989 *{published data only}*

Van Merode T, Van Bortel LM, Smeets FA, Mooij JM, Bohm RO, Rahn KH, et al. Verapamil and nebivolol improve carotid artery distensibility in hypertensive patients. *Journal of Hypertension - Supplement* 1989;**7**(6):S262-3.

Van Nueten 1997 *{published data only}*

Van Nueten L, Dupont AG, Vertommen C, Goyvaerts H, Robertson JI. A dose-response trial of nebivolol in essential hypertension. *Journal of Human Hypertension* 1997;**11**(2):139-44.

Van Nueten 1998 *{published data only}*

Van Nueten L, Taylor FR, Robertson JI. Nebivolol vs atenolol and placebo in essential hypertension: a double-blind randomised trial. *Journal of Human Hypertension* 1998;**12**(2):135-40.

Verdecchia 1983 *{published data only}*

Verdecchia P, Brignole M, Delfino G, Queirolo C, De Marchi G, Bertulla A, et al. Systolic time intervals as possible predictors of pressure response to sustained beta-adrenergic blockade in arterial hypertension. A within-patient, placebo-controlled study. *Hypertension* 1983;**5**(1):140-6.

Verdecchia 1988 *{published data only}*

Verdecchia P, Gatteschi C, Benemio G, Boldrini F, Guerrieri M, Porcellati C, et al. Duration of the antihypertensive action of atenolol, enalapril and placebo: a randomized within-patient study using ambulatory blood pressure monitoring. *International Journal of Clinical Pharmacology, Therapy, & Toxicology* 1988;**26**(11):570-4.

Weiss 2007 *{published data only}*

(2007). Erratum. *The Journal of Clinical Hypertension* 2007;**9**:806. [DOI: 10.1111/j.1751-7176.2007.tb00010.x]

* Weiss RJ, Weber MA, Carr AA, Sullivan WA. A randomized, double-blind, placebo-controlled parallel-group study to assess the efficacy and safety of nebivolol, a novel beta-blocker, in patients with mild to moderate hypertension. *Journal of Clinical Hypertension* 2007;**9**(9):667-76.

Williams 1992 *{published data only}*

William RL, Goyle KK, Herman TS, Rofman BA, Ruoff GE, Hogan LB. Dose-dependent effect of betaxolol in hypertension: A double-blind, multicenter study. *Journal of Clinical Pharmacology* 1992;**32**:360-7.

Wing 1988 *{published data only}*

Wing LM, Chalmers JP, West MJ, Russell AE, Morris MJ, Cain MD, et al. Enalapril and atenolol in essential hypertension: attenuation of hypotensive effects in combination. *Clinical & Experimental Hypertension - Part A, Theory & Practice* 1988;**10**(1):119-33.

References to studies excluded from this review

Wald 2008 *{published data only}*

Wald DS, Law M, Mills S, Bestwick JP, Morris JK, Wald NJ. A 16-week, randomized, double-blind, placebo-controlled, crossover trial to quantify the combined effect of an angiotensin-converting enzyme inhibitor and a beta-blocker on blood pressure reduction. *Clinical Therapeutics* 2008;**30**:2030-9.

Additional references

Chen 2010

Chen JMH, Heran BS, Perez MI, Wright JM. Blood pressure lowering efficacy of beta-blockers as second-line therapy for primary hypertension. *Cochrane Database of Systematic Reviews* 2010, Issue 1. [DOI: 10.1002/14651858.CD007185.pub2]

Chen 2010b

Chen N, Zhou M, Yang M, Guo J, Zhu C, Yang J, et al. Calcium channel blockers versus other classes of drugs for hypertension. *Cochrane Database of Systematic Reviews* 2010, Issue 8. [DOI: 10.1002/14651858.CD003654.pub4]

Deeks 2011

Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

eCPS

Canadian Pharmacist Association. https://www.e-therapeutics.ca/cps.showMonograph.action Accessed October 2012.

FDA

FDA Online Label Repository. http://labels.fda.gov/ Accessed May 2013.

Fitzgerald 1991

Fitzgerald JD. The applied pharmacology of beta-adrenoceptor antagonists (beta blockers) in relation to clinical outcomes. *Cardiovascular drugs and therapy* 1991;**5**:561-576.

Heran 2008a

Heran BS, Wong MMY, Heran IK, Wright JM. Blood pressure lowering efficacy of angiotensin converting enzyme (ACE) inhibitors for primary hypertension. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD003823.pub2]

Heran 2008b

Heran BS, Wong MMY, Heran IK, Wright JM. Blood pressure lowering efficacy of angiotensin receptor blockers for primary hypertension. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD003822.pub2]

Higgins 2011a

Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Higgins 2011b

Higgins JPT, Deeks JJ, Altman DG (editors). Chapter 16: Special topics in statistics. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Kamp 2000

Kamp TJ, Hell JW. Regulation of Cardiac L-Type Calcium Channels by Protein Kinase A and Protein Kinase C. *Circulation Research.* 2000;**87**:1095-102.

Lancaster 1988

Lancaster SG, Sorkin EM. Bisoprolol: a preliminary review of its pharmacodynamic and pharmacokinetics properties and therapeutics efficacy in hypertension and angina pectoris. *Drugs* 1988;**36**:256-85.

Law 2005

Law M, Morris JK, Jordan R, Wald N. Headaches and the treatment of blood pressure results from a meta-analysis of 94 randomized placebo-controlled trials with 24 000 participants. *Circulation* 2005;**112**:2301-2306.

Magee 2003

Magee LA, Duley L. Oral beta-blockers for mild to moderate hypertension during pregnancy. *Cochrane Database of Systematic Reviews* 2003, Issue 1. [DOI: 10.1002/14651858.CD002863]

Musini 2008

Musini VM, Fortin PM, Bassett K, Wright JM. Blood pressure lowering efficacy of renin inhibitors for primary hypertension. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD007066.pub2]

Musini 2014

Musini VM, Nazer M, Bassett K, Wright JM. Blood pressure-lowering efficacy of monotherapy with thiazide diuretics for primary hypertension. *Cochrane Database of Systematic Reviews* 2014, Issue 5. [DOI: 10.1002/14651858.CD003824.pub2]

Ravid 1985

Ravid M, Lang R, Jutrin I. The relative antihypertensive potency of propranolol, oxpranolol, atenolol and metoprolol given once daily. *Archive Internal Medicine* 1985;**145**:1321-3.

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Sterne 2011

Sterne JAC, Egger M, Moher D (editors). Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Intervention.* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Veverka 2006

Veverka A, Nuzum DS, Jolly JL. Nebivolol: A third generation beta adrenergic blocker. *Annals of Pharmacotherapy* 2006 Jul-Aug;**40**(7-8):1353-60. [PUBMED: 16822893]

Westfall 2011

Westfall TC, Westfall DP. Ch. 8 Neurotransmission: The autonomic and somatic motor nervous systems. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12. The McGraw-Hill Companies, Inc , 2011.

Wiysonge 2012

Wiysonge CS, Bradley HA, Volmink J, Mayosi BM, Mbewu A, Opie LH. Beta-blockers for hypertension. *Cochrane Database of Systematic Reviews* 2012, Issue 11. [DOI: 10.1002/14651858.CD002003.pub4]

Wong 2014a

Wong GWK, Wright JM. Blood pressure lowering efficacy of nonselective beta-blockers for primary hypertension. *Cochrane Database of Systematic Reviews* 2014, Issue 2. [DOI: 10.1002/14651858.CD007452.pub2]

Wong 2014b

Wong GWK, Boyda HN, Wright JM. Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension. *Cochrane Database of Systematic Reviews* 2014, Issue 11. [DOI: 10.1002/14651858.CD007450.pub2]

Wong 2015

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. [DOI: 10.1002/14651858.CD007449.pub2]

Wright 2000

Wright JM. Choosing a first-line drug in the management of elevated blood pressure: What is the evidence? 2: β-Blockers. *Canadian Medical Association Journal* 2000;**163**(2):188-192.

Wright 2009

Wright JM, Musini VM. First-line drugs for hypertension. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD001841.pub2]

Xue 2015

Xue H, Lu Z, Tang WL, Pang LW, Wang GM, Wong GWK, Wright JM. First-line drugs inhibiting the renin angiotensin system versus other first-line antihypertensive drug classes for hypertension. *Cochrane Database of Systematic Reviews* 2015, Issue 1. [DOI: 10.1002/14651858.CD008170.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ades 1990

Methods	Randomised, double-blinded, placebo-controlled parallel study, 11-week treatment period
Participants	N = 30, 22 men, mean age = 47 years, mean baseline BP 145/94 mmHg, primary hypertension
Interventions	Metoprolol 100 mg once daily, propranolol 80 mg once daily, placebo
Outcomes	SBP, DBP, heart rate, exercise training, cardiac output, echocardiogram, muscle biopsy
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	Unclear risk	Placebo was used
Blinding of outcome assessment (detection bias)	Unclear risk	No information

Ades 1990 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	Did not report withdrawal due to adverse effects

Ameling 1991

Methods	Randomised, double-blinded, placebo-controlled, cross-over study. Patients were seen for the first two weeks and BP was measured in every visit. Patients who were eligible, were randomised after week 2. Each treatment period lasted for four weeks and then patients crossed-over to another treatment for another four weeks. BP was measured in two-week intervals during the treatment period
Participants	Previously undiagnosed patients who had mean office DBP > 95 mmHg in two office visits, during the first two weeks, were included in the study. The study randomised 331 patients (188, 56.8% male) to betaxolol or placebo. Mean age = 50 years. Baseline SBP = 167.4 mmHg, DBP = 104.7 mmHg, heart rate = 80.3 bpm Exclusion criteria: age < 20 years or > 70 years; SBP > 190 mmHg or DBP > 125 mmHg; use of any medication that may affect BP; pregnancy; use of oral contraceptive; heart failure; bradycardia; chronic hepatic, renal or metabolic diseases; bronchial asthma; chronic pulmonary diseases
Interventions	Participants were randomised to betaxolol 20 mg once daily fixed dose (N = 163) or placebo (N = 168) for four weeks, and then crossed over.
Outcomes	Quality of life SBP, DBP, heart rate Withdrawal due to adverse effects
Notes	SD of BP measurements were not reported. SD were imputed using the weighted mean SD of studies in this review

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	High risk	"Subjects who were withdrawn from the study had no systematic follow up of their Quality of life assessment." There was no information about the follow up on SBP, DBP or heart rate data.

Ameling 1991 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal due to adverse effects was reported
Selective reporting (reporting bias)	Low risk	SBP, DBP, heart rate were reported without SD

Asmar 1991

Methods	Randomised, double-blinded, placebo-controlled cross-over study. Four-week treatment period
Participants	N = 14, 7 men, mean age = 53, baseline BP 156/101, primary hypertensive patients
Interventions	Bisoprolol 10 mg once daily, placebo
Outcomes	Resting BP, heart rate, haemodynamic parameters, pulse wave velocity determinations
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 and automated machine was used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Automated machine was used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on dropouts
Selective reporting (reporting bias)	Low risk	All outcomes reported

Baez 1986

Methods	Randomised, double-blinded, placebo-controlled parallel study. Three-week run in, 10-week treatment periods
Participants	N = 36, 24 men, age 33 years to 68 years Exclusion: haematological, renal, hepatic, gastrointestinal, autoimmune or cardiac diseases

Baez 1986 *(Continued)*

Interventions	Atenolol 50 mg, 100 mg once daily (only 50 mg data used), doxazosin 16 mg once daily, placebo
Outcomes	SBP, DBP, lab analysis
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	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	All outcomes reported

Bateman 1979

Methods	Randomised, double-blinded, placebo-controlled cross-over study, four-week treatment periods
Participants	N = 15, 11 men, age range 31 years to 64 years. Primary hypertension, without history of gout, chronic obstructive pulmonary disease, diabetes, ischaemic heart disease
Interventions	Atenolol 100 mg once daily, chlorthalidone 25 mg once daily, combination of two drugs, placebo
Outcomes	SBP, DBP, ambulatory blood pressure monitoring, biochemical analysis
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	All tablets were identical in appearance and taste

Bateman 1979 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was used
Blinding of outcome assessment (detection bias) All outcomes	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts were not included in the analysis
Selective reporting (reporting bias)	Low risk	All outcomes reported

Bengtsson 1976

Methods	Randomised, double-blinded, placebo-controlled cross-over study, four-week treatment period
Participants	N = 24, all women, mean age is 56 years, mean baseline BP 183/107 mmHg. Primary hypertension with normal renal function
Interventions	Metoprolol 40 mg thrice daily or placebo
Outcomes	SBP, DBP, heart rate, lab parameters
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	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts, 96% of tablets were taken
Selective reporting (reporting bias)	Low risk	All outcomes reported

Berglund 1985

Methods	Randomised, double-blinded, parallel study, four-week wash out, four-week treatment
Participants	N = 31, 24 male, mean age = 51.4 years, BP range 150-200/100-115 mmHg
Interventions	Pafenolol 25mg or 50 mg once daily, placebo
Outcomes	Casual BP, heart rate, 24 hour BP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	No information, but baseline was balanced
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was used, but no description on placebo tablet
Blinding of outcome assessment (detection bias) All outcomes	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	Did not mention withdrawal due to adverse effects as outcome, however, no patients dropped out

Broekman 1992

Methods	Randomised, double-blinded, cross-over study. six-week treatment period
Participants	N = 13, all men, mean age 51.2 years
Interventions	Bisoprolol 5 mg once daily, placebo
Outcomes	SBP, DBP, heart rate, sexual information
Notes	Group 1 only

Risk of bias

Bias	Authors' judgement	Support for judgement

Broekman 1992 *(Continued)*

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	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information
Selective reporting (reporting bias)	Low risk	Did not report baseline. Other outcomes were reported

Chan 1991

Methods	Randomised, double-blinded, placebo-controlled parallel study. four-week run in, week four-treatment period
Participants	N = 29, seven men, mean age = 46 years, mean baseline BP 163/106 mmHg, primary hypertension, normal renal function, without insulin dependent diabetes and secondary hypertension
Interventions	Nebivolol 5 mg once daily, placebo
Outcomes	BP, heart rate biochemistry, chest X-ray, electrocardiography, quality of life
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	Matching placebo was used
Blinding of outcome assessment (detection bias) All outcomes	High risk	Did not use automated machine

Chan 1991 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	All outcomes reported

Chan 1992

Methods	Randomised, double-blinded, placebo-controlled parallel study. four-week run-in, four-week treatment period
Participants	N = 32, eight men, mean age = 47 years, mean baseline BP = 164/105.8 mmHg. Primary hypertension, without renal disease, diabetes, secondary hypertension
Interventions	Nebivolol 5 mg once daily, placebo
Outcomes	Rest SBP, DBP, heart rate, plasma biochemistry, plasma renin and hormone level
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	Matching placebo tablet was used
Blinding of outcome assessment (detection bias) All outcomes	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	All outcomes reported

Chrysant 1992

Methods	Randomised, double-blinded, placebo-controlled parallel study, three-week run in, four-week treatment period

Chrysant 1992 *(Continued)*

Participants	N = 256, 120 men, mean age 53 years, mean baseline BP 152.5/103 mmHg. Primary hypertension without renal failure, congestive heart failure, lung diseases, liver diseases or blood diseases. Women of child bearing age were excluded
Interventions	Atenolol 25 mg, 50 mg once daily, hydrochlorothiazide 25 mg/triamterene 50 mg once daily, their combinations, placebo
Outcomes	SBP, DBP, heart rate, withdrawal due to adverse effects
Notes	Withdrawal due to adverse effects not reported according to treatment groups

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	Unclear risk	Placebo was used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Eight withdrawals in total
Selective reporting (reporting bias)	Low risk	All outcomes reported

Cilliers 1979

Methods	Randomised, double-blinded, placebo-controlled cross-over study, four-week treatment periods
Participants	N = 50, 29 men, mean age 47 years, mean baseline BP 165.8/107.7 mmHg. Primary hypertension, never-been-treated patients
Interventions	Atenolol 100 mg once daily, placebo
Outcomes	SBP, DBP, heart rate, withdrawal due to adverse effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Cilliers 1979 *(Continued)*

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	High risk	Did not used automated machine
Incomplete outcome data (attrition bias) All outcomes	Low risk	Nine dropouts, three withdrawal due to adverse effects
Selective reporting (reporting bias)	Low risk	All outcomes reported

Dahlof 1986

Methods	Multicenter, randomised, double-blinded, parallel studies, four-week run in, four-week treatment
Participants	N = 23, 12 men, mean age = 49 years, primary hypertensive, mean BP 164/109 mmHg
Interventions	Pafenolol 50 mg or 100 mg once daily, placebo
Outcomes	Rest and exercise BP, heart rate, dropouts
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	No information, but baseline groups were balanced
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was used. But no description on the placebo tablet
Blinding of outcome assessment (detection bias) All outcomes	High risk	Did not use automated machine
Incomplete outcome data (attrition bias)	Unclear risk	All patients were accounted for. Did not mention the procedure to process dropout patients

Dahlof 1986 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	All outcomes reported

Davidov 1994

Methods	Multi-center, randomised, double-blinded, placebo-controlled parallel study. Four-week to six-week run in period, four-week treatment period
Participants	N = 276, 70% men, mean age = 53 years, mean baseline BP 149/100 mmHg, primary hypertension without any condition that might influence blood pressure
Interventions	Bisoprolol 5 mg, 10 mg, 20 mg once daily, placebo
Outcomes	SBP, DBP, heart rate
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	No information but baseline was balanced
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	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on withdrawal
Selective reporting (reporting bias)	High risk	Did not report withdrawals due to adverse effects

Deary 2001

Methods	Randomised, double-blinded, placebo-controlled cross-over study, two-week run in, six-week treatment
Participants	N = 34, 25 men, mean age= 47 years, DBP between 95 and 110 mmHg in three readings in 3 months.

Deary 2001 *(Continued)*

Interventions	Bisoprolol 5 mg once daily, amlodipine 5 mg once daily, doxazosin 1 mg to 4 mg once daily, lisinopril 2.5 mg to 10 mg once daily, bendrofluazide 2.5 mg once daily, placebo
Outcomes	Resting BP, quality of life, ambulatory blood pressure monitoring, left ventricular function
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomized with Latin square"
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Physician determined which "best" treatment was repeated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Automated machine was used
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	All outcomes reported

Deary 2002

Methods	Randomised, double-blinded, placebo-controlled, cross-over study. Two-week run-in, six-week treatment
Participants	N = 30, 22 men, DBP > 95 mmHg after run in
Interventions	Bisoprolol 5 mg once daily, amlodipine 5 mg once daily, doxazosin 4 mg once daily, lisinopril 10 mg once daily, bendrofluazide 2.5 mg once daily, placebo
Outcomes	BP, heart rate, central BP, plasma atrial natriuretic peptide, pulse wave analysis
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information

Deary 2002 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	High risk	The best treatment was repeated after rotation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Automated machine was used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information
Selective reporting (reporting bias)	Low risk	All outcomes reported

Dhakam 2008

Methods	Randomised, double-blinded, placebo-controlled cross-over study, two-week run in, five-week treatment period
Participants	N = 16, 10 men, mean age 70 years, mean baseline BP 158/84 mmHg. Never-treated subjects without secondary hypertension, diabetes, renal impairment
Interventions	Atenolol 50 mg once daily, nebivolol 5 mg once daily, placebo
Outcomes	SBP, DBP, heart rate, aortic augmentation index, biochemical analysis
Notes	Isolated systolic hypertension

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	Automated machine was used
Incomplete outcome data (attrition bias) All outcomes	High risk	Did not mention dropouts

Dhakam 2008 *(Continued)*

Selective reporting (reporting bias)	Low risk	Did not report withdrawal due to adverse effects

Frishman 1995

Methods	Multi-centre, randomised, double-blinded placebo-controlled parallel study. Four-week to six-week run in period, four-week treatment period
Participants	N = 509, 245 men, mean baseline BP = 151/100 mmHg, primary hypertension, no more than 10% below or 35% above ideal weight
Interventions	Bisoprolol 5 mg once daily, hydrochlorothiazide 25 mg once daily, B5/H25 combination, placebo
Outcomes	SBP, DBP, heart rate, withdrawal due to adverse effects
Notes	It was unclear to which group participants who withdrew due to adverse effects belonged.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	No information, but baseline was balanced
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo tablet was used at the same frequency
Blinding of outcome assessment (detection bias) All outcomes	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Low risk	Did not report how they dealt with dropouts, but dropout rate was low
Selective reporting (reporting bias)	High risk	Withdrawal due to adverse effects was not reported based on treatment group

Frishman 2006

Methods	Randomised, double-blinded, placebo-controlled parallel study, four-week to five-week run in, nine-week treatment period
Participants	N = 1092, 57% men, mean age = 54, mean baseline BP 152.6/99.9 mmHg, primary hypertension without previous cardiovascular event or contraindication to beta blockers
Interventions	Metoprolol 25 mg, 100 mg, 400 mg once daily, felodipine 2.5 mg, 10 mg, 20 mg, any of the combination of metoprolol and felodipine listed or placebo

Frishman 2006 *(Continued)*

Outcomes	Rest trough SBP, DBP, safety
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Each centre has blocks of patients randomised to a group
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double dummy design
Blinding of outcome assessment (detection bias) All outcomes	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Low risk	11% of all patients dropouts. ITT analysis
Selective reporting (reporting bias)	Low risk	All outcomes reported, did not report withdrawal due to adverse effects according to treatment groups

Frisk-Holmberg 1985

Methods	Randomised, double-blinded, placebo-controlled cross-over study, three-week run in, six-week treatment periods
Participants	N = 8, all men, primary hypertension
Interventions	Atenolol 100 mg twice daily, placebo
Outcomes	Exercise/rest haemodynamic, metabolic effect
Notes	Did not report SBP, DBP

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

Frisk-Holmberg 1985 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was used
Blinding of outcome assessment (detection bias) All outcomes	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	High risk	Did not mention dropouts
Selective reporting (reporting bias)	High risk	Did not report SBP, DBP, withdrawal due to adverse effects

Giles 2014

Methods	Randomised, double-blinded, placebo-controlled parallel study, six-week run in, eight-week treatment period
Participants	Mean SBP/DBP is 155/100 mmHg, mean age 51 years, mild to moderate hypertensive patients. 4161 randomized, 1386 to monotherapy groups
Interventions	Nebivolol 10 mg/day and 40 mg/day, valsartan 160 mg/day and 320 mg/day, nebivolol and valsartan combination 10/160 mg/day, 10/320 mg/day, 20/320 mg/day and placebo
Outcomes	Change of SBP, DBP and heart rate, withdrawal due to adverse effects
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomisation codes were generated by the Statistical Programming Department at the Forest Research Institute (Jersey City, NJ, USA) and implemented (including the maintenance of masking) by a 24-h interactive web response system."
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Tablets were identical in appearance, taste, and smell, and participants and research staff were masked to study drug treatment for the duration of the trial."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Automated machine was used
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was less than 10%

Giles 2014 *(Continued)*

Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported

Gostick 1977

Methods	Randomised, double-blinded, placebo-controlled cross-over study, 12-week run in, four-week treatment period each
Participants	N = 98, 84 were available for analysis, mean age 50.1 years, mean baseline BP 165.6/101.9 mmHg. Mild to moderate hypertension
Interventions	Atenolol 50 mg, 100 mg, 200 mg once daily, placebo
Outcomes	SBP, DBP, heart rate, blood urea, uric acid, serum electrolytes
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Latin square design
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	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Low risk	14 dropouts, all patients accounted for
Selective reporting (reporting bias)	Low risk	All outcomes reported

Gudbjornsdottir 1997

Methods	Randomised, double-blinded, placebo-controlled cross-over study, three-week run in, six-week treatment period
Participants	N = 7, four men, mean age = 52 years, mean baseline BP 154/97. Primary hypertension diagnosed for at least one year, normal ECG, blood count, serum electrolyte, normal liver and renal function
Interventions	Metoprolol 100 mg twice daily, placebo

Gudbjornsdottir 1997 *(Continued)*

Outcomes	SBP, DBP, blood glucose, hormone
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	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information
Selective reporting (reporting bias)	High risk	Did not report dropouts

Hansson 1975

Methods	Randomised, double-blinded, placebo-controlled parallel study, 16-week treatment periods (data for weeks 4, 8 and 12 were reported and used in analysis)
Participants	N = 45, 26 men, mean age 46 years, mean baseline BP 169/106 mmHg. Primary hypertension
Interventions	Atenolol 50 mg twice daily, placebo
Outcomes	SBP, DBP, heart rate, withdrawal due to adverse effects
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

Hansson 1975 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was used
Blinding of outcome assessment (detection bias) All outcomes	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient withdrew
Selective reporting (reporting bias)	Low risk	All outcomes reported

Himmelmann 1996

Methods	Randomised, double-blinded, placebo-controlled cross-over study. Four-week run in, four-week treatment period
Participants	N = 14. 12 men and 3 women, mean age 50 years, 95 < DBP < 110 mmHg, primary hypertension
Interventions	Nebivolol 5 mg once daily, placebo
Outcomes	SBP, DBP, heart rate, ambulatory blood pressure monitoring, blood chemistry
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	Unclear risk	Did not use machine
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Did not mention dropouts
Selective reporting (reporting bias)	High risk	Withdrawal due to adverse effects was not reported

Houston 1990

Methods	Randomised, double-blinded, placebo-controlled parallel study, two-week to four-week run in, eight-week treatment period
Participants	N = 92, 61% men, mean age 48 years, mean baseline BP 140/96.5 mmHg. Primary hypertension without renal, hepatic disease, neoplastic or peripheral vascular diseases
Interventions	Atenolol 25 mg, 50 mg twice daily (only 50 mg twice daily result was available), clonidine 0.1 mg, 0.2 mg twice daily, placebo
Outcomes	SBP, DBP, serum lipid
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	High risk	
Selective reporting (reporting bias)	High risk	

Jaattela 1990

Methods	Randomised, double-blinded, placebo-controlled parallel study, two-week run in, four-week treatment period. This publication contained two studies with two sets of patients, we combined their data as one RCT
Participants	N = 99, 45 men, mean age = 59 years, mean baseline BP 169/101 mmHg, primary hypertension, without heart failure, diabetes and asthma
Interventions	Metoprolol 50 mg once daily, placebo
Outcomes	SBP, DBP, heart rate, response rate, safety
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information

Jaattela 1990 *(Continued)*

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	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Low risk	Did not report dropouts, but only three patients' data were missing at the end
Selective reporting (reporting bias)	High risk	Did not report withdrawal due to adverse effects

Jeffers 1977

Methods	Randomised, double-blinded, placebo-controlled cross-over study, four-week run in, four-week treatment period
Participants	N = 21, eight men, mean age 53 years, mean baseline BP 161.7/111.5 mmHg
Interventions	Atenolol 50 mg, 100 mg, 200 mg once daily, placebo
Outcomes	SBP, DBP, heart rate
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Order of administration was determined by a random code
Allocation concealment (selection bias)	Low risk	Participant received pre-packed container
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Automated machine was used
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two participants dropped out

Jeffers 1977 *(Continued)*

Selective reporting (reporting bias)	Low risk	Withdrawal due to adverse effects was reported but not according to treatment group

Lacourciere 1994

Methods	Randomised, double-blinded, placebo-controlled parallel study. Eight-week run-in, 12-week treatment period
Participants	N = 240 (226 completed), 95 < DBP < 110 mmHg, mild to moderate primary hypertension
Interventions	Nebivolol 1 mg, 5 mg, 10 mg once daily, Hydrochlorothiazide 12.5 mg, 25, mg once daily, every possible combination of the two drugs, placebo
Outcomes	SBP, DBP, lipids, lipoprotein, apolipoprotein, routine lab parameters
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	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Low risk	Did not report the procedure to deal with dropout data. But only 6% patients dropped out
Selective reporting (reporting bias)	Low risk	Did not report withdrawal due to adverse effects or heart rate

Lepantalo 1983

Methods	Randomised, double-blinded, placebo-controlled cross-over study. Four-week run in, four-week treatment period
Participants	N = 34, 17 men, mean age = 54.1 years, mean baseline BP 160/100, primary hypertension
Interventions	Metoprolol 100 mg twice daily, propranolol 80 mg twice daily, placebo
Outcomes	SBP, DBP, peripheral vascular resistance

Lepantalo 1983 *(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	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	Did not report withdrawal due to adverse effects

Lischner 1987

Methods	Randomised, double-blinded, placebo-controlled cross-over study, two-week run in, four-week treatment periods
Participants	N = 128, 60 men, mean age 54 years for women, 52 years for men, mean baseline BP 167/111.3 mmHg. Primary hypertension without hepatic or renal diseases, obesity
Interventions	Atenolol 100 mg once daily, amiloride 5 mg/hydrochlorothiazide 50 mg once daily, placebo
Outcomes	SBP, DBP, heart rate
Notes	Data for women and men were reported separately. We combined the data according to the recommendation of the *Cochrane Handbook for Systematic Reviews of Interventions*

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

Lischner 1987 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was used
Blinding of outcome assessment (detection bias) All outcomes	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data of withdrawn patients were not included
Selective reporting (reporting bias)	Low risk	All outcomes reported

Maclean 1990

Methods	Randomised, double-blinded, placebo-controlled parallel study, three-week run in, six-week treatment period
Participants	N = 136, primary hypertensive patients. Exclusion: renal or hepatic impairment, COPD, diabetes, peripheral vascular diseases, heart failure, heart block, myocardial infarction
Interventions	Atenolol 50 mg once daily, nitrendipine 20 mg once daily, atenolol 50 mg/nitrendipine 20 mg, placebo
Outcomes	SBP, DBP, adverse effects
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 design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was used
Blinding of outcome assessment (detection bias) All outcomes	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Low risk	11 patients dropped out. All reasons were stated
Selective reporting (reporting bias)	Low risk	All outcomes reported

Myers 1983

Methods	Randomised, double-blinded, placebo-controlled cross-over study, six-week treatment period
Participants	N = 12, eight men, mean age 52.8 years, mean baseline BP 173/109 mmHg. Primary hypertension, without atrioventricular block, history of hepatic or renal diseases, diabetes, alcoholism, asthma, myocardial infarction, stroke, congestive heart failure, bradycardia.
Interventions	Atenolol 100 mg once daily, hydrochlorothiazide 50 mg once daily, placebo
Outcomes	SBP, DBP, heart rate, biochemical test
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	Double dummy design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three patients dropped out, their data were not included in analysis
Selective reporting (reporting bias)	High risk	Dropouts were reported, but did not provide reason

NEB-305

Methods	Multi-center, randomised, double-blinded, placebo-controlled, parallel study, 12-week treatment period
Participants	N = 807, 53.5% men, mean age = 53.4 years, mean baseline BP 151/99 mmHg. Primary hypertension, without asthma and COPD, renal and liver diseases, insulin dependent diabetes
Interventions	Nebivolol 5 mg, 10 mg, 20 mg once daily, placebo
Outcomes	Rest peak/trough SBP, DBP, withdrawal due to adverse effects, response rate
Notes	

Risk of bias

NEB-305 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	No information, however, the baseline demographic was similar in each group
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo was used
Blinding of outcome assessment (detection bias) All outcomes	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for. Analysis was ITT LOCF
Selective reporting (reporting bias)	Low risk	All outcomes reported

Okawa 1986

Methods	Randomised, double-blinded, placebo-controlled parallel study. After four weeks of placebo washout, patients were randomised to treatment. During the first two weeks of treatment, patients randomised to high dose were force titrated to respective dosage. After that, doses were fixed for the duration of next six weeks
Participants	N = 139 (87 male) 100 mmHg < DBP < 120 mmHg
Interventions	Bevantolol 50 mg twice daily, 100 mg twice daily, 150 mg twice daily, 200 mg twice daily or placebo
Outcomes	SBP, DBP, heart rate, withdrawal due to adverse effects, adverse effect, clinical lab
Notes	Three withdrawalw due to adverse effects in bevantolol, none in placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	No information, but baseline was balanced
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebos were given at the same frequency as active treatment

Okawa 1986 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on follow up
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal due to adverse effects were reported
Selective reporting (reporting bias)	Low risk	Haemodynamic data were primary outcomes, withdrawal due to adverse effects were reported in detail

Papademetriou 2006

Methods	Multicenter, randomised, double-blinded, placebo-controlled, parallel study. Four-week to five-week run in, eight-week treatment period
Participants	N = 1571, 51% men, mean age = 53 years, mean baseline BP 151/100 mmHg. Primary hypertension without heart failure, recent MI, contraindication for beta blockers
Interventions	Metoprolol 25 mg, 50 mg, 100 mg, 200 mg once daily, Hydrochlorothiazide 6.25 mg, 12.5 mg, 25 mg once daily, any combination of the two drugs, placebo
Outcomes	Trough SBP, DBP, haematology, lipid, urinalysis, ECG
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central, computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Interactive voice response system allocated patients to treatment groups
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double dummy design
Blinding of outcome assessment (detection bias) All outcomes	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Low risk	2.9% withdrawal due to adverse effects, ITT analysis
Selective reporting (reporting bias)	High risk	Peak pressure was mentioned in protocol but not reported, withdrawal due to adverse effects was not reported according to treatment groups

Petrie 1976

Methods	Randomised, double-blinded, placebo-controlled cross-over study. After 14 days of washout period, patients were randomised to a sequence of four-week treatments
Participants	N = 24 (13 male) 105 < DBP < 125 mmHg Exclusion: recent MI, evidence of heart failure, heart block, gross ischaemia, grade III or IV retinopathy, diabetes, gout, impaired liver function, or creatinine clearance less than 60 ml/min or if they were on any other drug treatment
Interventions	Methyldopa 250 mg thrice daily, practolol 200 mg thrice daily, propranolol 80 mg thrice daily, methyldopa 250 mg and propranolol 80 mg thrice daily, methyldopa 250 mg and practolol 200 mg thrice daily or placebo
Outcomes	SBP, DBP, heart rate, quality of life
Notes	SD were imputed using the average of other studies that provided SD

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Low risk	Drug packages were pre-packed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants took the same number of pills
Blinding of outcome assessment (detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	High risk	SD were not reported

Petrie 1980

Methods	Randomised, double-blinded, placebo-controlled cross-over study, four-week run in, four-week treatment periods
Participants	N = 23, 12 men, mean age 40.9 years, mean baseline BP 155/109.4 mmHg.
Interventions	Atenolol 100 mg once daily, oxprenolol 160 mg once daily, propranolol 160 mg once daily, placebo
Outcomes	SBP, DBP

Petrie 1980 *(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	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	High risk	Did not report dropouts
Selective reporting (reporting bias)	High risk	Did not report withdrawal due to adverse effects

Rosen 1994

Methods	Randomised, double-blinded, placebo-controlled cross-over study, four-week run in, four-week treatment periods
Participants	N = 21, all men, age range 31 years to 70 years, mean baseline BP 157/101.9 mmHg
Interventions	Atenolol 100 mg once daily, propranolol 80 mg twice daily, alpha-methyldopa 500 mg twice daily, hydrochlorothiazide/triamterene 50 mg/25 mg twice daily, placebo
Outcomes	SBP, DBP, sleep assessment, sexual function questionnaire
Notes	8 of 21 patients withdrew from the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Modified Latin square
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias)	High risk	No indication that placebo was used at same frequency

Rosen 1994 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	High risk	40% of patient dropouts
Selective reporting (reporting bias)	Low risk	All outcomes reported

Saunders 2007

Methods	Multi-center, randomised, double-blinded, placebo-controlled, parallel study. Four-week run-in, 12-week treatment period
Participants	N = 300, 45.3% men, mean age = 50.9 years, mean baseline BP 152.2/100.2 mmHg. Primary hypertensive, BMI < 40, no cardiovascular condition or diabetes
Interventions	Nebivolol 2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg once daily, placebo
Outcomes	Rest peak/trough SBP, DBP, heart rate, ECG, lab parameters
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	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT LOCF was used for analysis
Selective reporting (reporting bias)	Low risk	All outcomes reported

Seedat 1980

Methods	Randomised, double-blinded, placebo-controlled cross-over study, four-week treatment period
Participants	N = 24, Africans with primary hypertension. Exclusion criteria: heart failure, asthma, MI, heart block, pregnancy, impaired renal and hepatic function
Interventions	Atenolol 100 mg once daily, chlorthalidone 25 mg once daily, combination of two drugs, placebo
Outcomes	SBP, DBP, heart rate, plasma renin activity, serum potassium
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	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Did not mention dropouts
Selective reporting (reporting bias)	High risk	Withdrawal due to adverse effects was not mentioned

Stornello 1991

Methods	Randomised, double-blinded, placebo-controlled cross-over study, three-week run in, six-week treatment periods
Participants	N = 12, four men, mean age 51.9 years, primary hypertension with non–insulin-dependent diabetes mellitus, persistent aluminuria, no evidence of urinary tract infection, other kidney disease
Interventions	Atenolol 50 mg once daily, enalapril 20 mg once daily, chlorthalidone 12.5 mg once daily, placebo
Outcomes	SBP, DBP, Heart rate, renal vascular resistance, filtration fraction, blood chemistry
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Stornello 1991 *(Continued)*

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	Automated machine was used
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	All outcomes reported

Stumpe 1985

Methods	Randomised, double-blinded, placebo-controlled parallel study, four-week run in, four-week treatment periods
Participants	N = 232. Exclusion: history of heart disease or asthma
Interventions	Atenolol 50 mg once daily, celiprolol 200 mg, 400 mg, 600 mg once daily, placebo
Outcomes	SBP, DBP
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 design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was used
Blinding of outcome assessment (detection bias) All outcomes	High risk	Did not use automated machine
Incomplete outcome data (attrition bias)	Unclear risk	Did not report dropout rate

Stumpe 1985 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	High risk	Did not report withdrawal due to adverse effects

Tonkin 1990

Methods	Randomised, double-blinded, placebo-controlled cross-over study, four-week run in, four-week treatment periods
Participants	N = 15, seven men, median age 61 years, primary hypertension patients. Exclusion criteria: diabetes, cardiac disease, COPD, impaired renal or hepatic function
Interventions	Atenolol 50 mg once daily, diltiazem 60 mg once daily, combination of two drugs, placebo
Outcomes	SBP, DBP, ECG, haematology, adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	4 x 4 Latin square design
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	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 dropouts
Selective reporting (reporting bias)	Low risk	All outcomes reported

Tseng 1993

Methods	Randomised, double-blinded, placebo-controlled parallel study. Two- week to four-week run in period, three-week treatment period
Participants	N = 65, 35 men, mean age = 51 years, mean baseline BP 160/101 mmHg, primary hypertension without any co-morbidity

Tseng 1993 *(Continued)*

Interventions	Bisoprolol 5 mg, 10 mg once daily or placebo
Outcomes	DBP, heart rate, response rate, biochemical haematological change, ECG
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	No information, but baseline was balanced
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	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	High risk	Did not report dropouts
Selective reporting (reporting bias)	High risk	Did not report SBP

Van Bortel 1993

Methods	Randomised, double-blinded, placebo-controlled cross-over study. Four-week run in, four-week treatment period
Participants	N = 114, 76 men, mean age = 54, 95 < DBP < 120 mmHg, primary hypertension, normal liver and renal function, no history of heart failure, severe vascular disease, uncontrolled diabetes
Interventions	Nebivolol 5 mg once daily, placebo
Outcomes	BP, heart rate, quality of life, ECG, lab parameters
Notes	Only 80 patients randomised to cross-over group

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

Van Bortel 1993 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was used
Blinding of outcome assessment (detection bias) All outcomes	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	All outcomes reported

Van Herwaarden 1977

Methods	Randomised, double-blinded, placebo-controlled cross-over study, four-week treatment period
Participants	N = 8, mean age = 34 years
Interventions	Metoprolol 100 mg thrice daily, propranolol 80 mg thrice daily, placebo
Outcomes	Rest and adrenaline infused SBP, DBP, heart rate
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	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	All outcomes reported

Van Merode 1989

Methods	Randomised, double-blinded, placebo-controlled cross-over study. Four-week run in, four-week treatment period
Participants	N = 29, 21 men, primary hypertension with normal kidney and liver functions
Interventions	Nebivolol 5 mg once daily, placebo
Outcomes	SBP, DBP, pulse pressure, carotid diameter and compliance
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	Identical placebo was used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Automated machine was used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Did not mention dropout
Selective reporting (reporting bias)	High risk	Did not report withdrawal due to adverse effects

Van Nueten 1997

Methods	Multi-centered, randomised, double-blinded, placebo-controlled, parallel study. Four-week run in, four-week treatment period
Participants	N = 509, 53% men, baseline mean BP 158.4/102.7 mmHg. Exclusion criteria: secondary hypertension, asthma and COPD, bradycardia, AV block, insulin dependent diabetes, MI or stroke in past six months, heart failure, renal hepatic disease, 50% over weight base on BMI
Interventions	Nebivolol 0.5 mg, 1 mg, 2.5 mg, 5 mg, 10 mg once daily, placebo
Outcomes	Rest peak/trough BP, ECG, lab parameters, symptom score, withdrawal due to adverse effects
Notes	

Risk of bias

Van Nueten 1997 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo tablets were identical in appearance and taste
Blinding of outcome assessment (detection bias) All outcomes	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Low risk	All dropouts reported, dropout rate was low
Selective reporting (reporting bias)	Low risk	All outcomes reported

Van Nueten 1998

Methods	Randomised, double-blinded, placebo-controlled parallel study, four-week run in, four-week treatment period
Participants	N = 364, 191 men, mean age = 55 years, mean baseline BP 166.5/104 mmHg. Primary hypertension, previously untreated or responded poorly to previous treatment
Interventions	Nebivolol 5 mg once daily, Atenolol 50 mg once daily, placebo
Outcomes	SBP, DBP, adverse event, ECG, blood chemistry, haematology, urine test
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All tablets were identical
Blinding of outcome assessment (detection bias)	High risk	Did not use automated machine

Van Nueten 1998 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 patients were lost to follow-up at the end
Selective reporting (reporting bias)	High risk	Did not report withdrawal due to adverse effects

Vanhees 1991

Methods	Randomised, double-blinded, placebo-controlled cross-over study, three-week run in, three-week treatment periods
Participants	N = 15, all men, mean age 39.4 years, mean baseline BP 166/93
Interventions	Atenolol 50 mg once daily, verapamil 240 mg once daily, enalapril 10 mg once daily, matching placebo
Outcomes	Exercise tolerance, rest SBP, DBP, exercise parameters, urine and blood analysis
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	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts were accounted for
Selective reporting (reporting bias)	Low risk	All outcomes reported

Verdecchia 1983

Methods	Randomised, double-blinded, placebo-controlled cross-over study, two-week placebo, four-week treatment period

Verdecchia 1983 *(Continued)*

Participants	N = 20, 14 men, mean age = 44 years, mean baseline BP 165.5/108.3, primary hypertension with normal ECG
Interventions	Metoprolol 200 mg once daily, placebo
Outcomes	SBP, DBP, heart rate, systolic time interval
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	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	All outcomes reported

Verdecchia 1988

Methods	Randomised, double-blinded, placebo-controlled cross-over study, three-week run in, four-week treatment periods
Participants	N = 12, five men, mean age 48.6 years, primary hypertension
Interventions	Atenolol 100 mg once daily, placebo
Outcomes	SBP, DBP, heart rate, ambulatory blood pressure monitoring, withdrawal due to adverse effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	4 x 4 Latin square design

Verdecchia 1988 *(Continued)*

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	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	All outcomes reported

Weiss 2007

Methods	Multi-center, randomised, double-blinded, placebo-controlled, parallel study. Two-week run-in, 12-week treatment period
Participants	N = 909, 57% men, mean age = 54.7 years, mean baseline BP 153.1/99.5 mmHg. Primary hypertensive, BMI < 35, no history of cardiovascular disease or diabetes
Interventions	Nebivolol 1.25 mg, 2.5mg , 5 mg, 10 mg, 20 mg, 40 mg once daily, placebo
Outcomes	Rest peak/trough SBP, DBP, heart rate, safety
Notes	Not all patients in 40 mg group took 40 mg, therefore we excluded this group

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	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data was presented as ITT LOCF

Weiss 2007 *(Continued)*

Selective reporting (reporting bias)	Low risk	All data reported

Williams 1992

Methods	Randomised, double-blinded, placebo-controlled parallel study. Participants entered a three-week to four-week placebo run in period, during which they were instructed to take the capsule at 10 am every morning. Patients who met the entry criteria were randomised to one of the 4 treatment groups for another five weeks. After the fixed dose period, there was a one-week follow-up period
Participants	N = 317 Patients with mean DBP between 95 mmHg and 110 mmHg during the run in period were eligible for randomization
Interventions	Betaxolol 5 mg, 10 mg, 20 mg once daily or placebo
Outcomes	SBP, DBP, heart rate, withdrawal, adverse effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	No information, but baseline was balanced
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo capsules were used in same frequency
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Withdrawn were accounted for and not included in analysis
Incomplete outcome data (attrition bias) All outcomes	Low risk	All reasons for withdrawal were reported
Selective reporting (reporting bias)	Low risk	All outcomes reported

Wing 1988

Methods	Randomised, double-blinded, placebo-controlled cross-over study, four-week run in, four-week treatment periods
Participants	N = 16, six men, mean age 59 years. Primary hypertension without target organ damage

Wing 1988 *(Continued)*

Interventions	Atenolol 50 mg once daily, enalapril 20 mg once daily, atenolol/enalapril combination, placebo
Outcomes	SBP, DBP, heart rate, blood chemical analysis
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	4 x 4 Latin square design
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	High risk	Did not use automated machine
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on dropouts
Selective reporting (reporting bias)	High risk	Did not report withdrawal due to adverse effects

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Wald 2008	Non-hypertensive and hypertensive participants were mixed and randomised. The data of hypertensive patients were not reported separately

DATA AND ANALYSES

Comparison 1. Nebivolol vs Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SBP	13		Mean Difference (Fixed, 95% CI)	Subtotals only

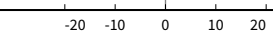
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 (0.25 x starting dose) 1.0 & 1.25 mg/day	3	366	Mean Difference (Fixed, 95% CI)	-4.49 [-7.15, -1.83]
1.2 (0.5 x starting dose) 2.5 mg/day	3	415	Mean Difference (Fixed, 95% CI)	-4.96 [-7.66, -2.26]
1.3 (starting dose) 5 mg/day	12	1280	Mean Difference (Fixed, 95% CI)	-8.81 [-10.23, -7.40]
1.4 (2 x starting dose) 10 mg/day	6	1684	Mean Difference (Fixed, 95% CI)	-6.04 [-7.47, -4.60]
1.5 (4 x starting dose) 20 mg/day	3	652	Mean Difference (Fixed, 95% CI)	-6.95 [-9.26, -4.63]
1.6 (8 x starting dose) 30, 40 mg/day	3	1155	Mean Difference (Fixed, 95% CI)	-8.10 [-9.84, -6.36]
2 DBP	13		Mean Difference (Fixed, 95% CI)	Subtotals only
2.1 (0.25 x starting dose) 1.0 & 1.25 mg/day	3	366	Mean Difference (Fixed, 95% CI)	-3.55 [-5.17, -1.93]
2.2 (0.5 x starting dose) 2.5 mg/day	3	415	Mean Difference (Fixed, 95% CI)	-4.23 [-5.76, -2.70]
2.3 (starting dose) 5 mg/day	12	1280	Mean Difference (Fixed, 95% CI)	-6.67 [-7.54, -5.80]
2.4 (2 x starting dose) 10 mg/day	6	1684	Mean Difference (Fixed, 95% CI)	-5.90 [-6.78, -5.01]
2.5 (4 x starting dose) 20 mg/day	3	652	Mean Difference (Fixed, 95% CI)	-5.81 [-7.21, -4.41]
2.6 (8 x starting dose) 30, 40 mg/day	3	1155	Mean Difference (Fixed, 95% CI)	-7.70 [-8.80, -6.61]
3 Heart rate	8		Mean Difference (Fixed, 95% CI)	Subtotals only
3.1 (0.25 x starting dose) 1.25 mg/day	1	136	Mean Difference (Fixed, 95% CI)	-2.9 [-5.86, 0.06]
3.2 (0.5 x starting dose) 2.5 mg/day	2	218	Mean Difference (Fixed, 95% CI)	-3.89 [-6.18, -1.61]
3.3 (starting dose) 5 mg/day	7	487	Mean Difference (Fixed, 95% CI)	-8.21 [-9.66, -6.76]
3.4 (2 x starting dose) 10 mg/day	3	1120	Mean Difference (Fixed, 95% CI)	-7.23 [-8.48, -5.99]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.5 (4 x starting dose) 20 mg/day	2	298	Mean Difference (Fixed, 95% CI)	-8.43 [-10.48, -6.38]
3.6 (8 x starting dose) 30, 40 mg/day	3	1155	Mean Difference (Fixed, 95% CI)	-10.94 [-12.18, -9.71]
4 Pulse Pressure	13		Mean Difference (Fixed, 95% CI)	Subtotals only
4.1 (0.25 x starting dose) 1.0 & 1.25 mg/day	3	366	Mean Difference (Fixed, 95% CI)	-0.88 [-3.21, 1.45]
4.2 (0.5 x starting dose) 2.5 mg/day	3	415	Mean Difference (Fixed, 95% CI)	-0.95 [-3.32, 1.41]
4.3 (starting dose) 5 mg/day	12	1314	Mean Difference (Fixed, 95% CI)	-1.62 [-2.83, -0.41]
4.4 (2 x starting dose) 10 mg/day	6	1684	Mean Difference (Fixed, 95% CI)	-0.19 [-1.47, 1.08]
4.5 (4 x starting dose) 20 mg/day	3	652	Mean Difference (Fixed, 95% CI)	-1.25 [-3.38, 0.89]
4.6 (8 x starting dose) 30, 40 mg/day	3	1155	Mean Difference (Fixed, 95% CI)	-0.37 [-1.94, 1.20]
5 Peak vs Trough SBP	4		Mean Difference (Fixed, 95% CI)	Subtotals only
5.1 (0.25 x starting dose) 1.0 & 1.25 mg/day	2	335	Mean Difference (Fixed, 95% CI)	0.30 [-1.90, 2.49]
5.2 (0.5 x starting dose) 2.5 mg/day	3	415	Mean Difference (Fixed, 95% CI)	-1.24 [-3.28, 0.81]
5.3 (starting dose) 5 mg/day	4	817	Mean Difference (Fixed, 95% CI)	1.40 [0.14, 2.66]
5.4 (2 x starting dose) 10 mg/day	4	822	Mean Difference (Fixed, 95% CI)	-0.17 [-1.42, 1.08]
5.5 (4 x starting dose) 20 mg/day	3	652	Mean Difference (Fixed, 95% CI)	1.17 [-0.27, 2.61]
5.6 (8 x starting dose) 30, 40 mg/day	2	331	Mean Difference (Fixed, 95% CI)	-1.20 [-3.19, 0.78]
6 Peak vs Trough DBP	4	3372	Mean Difference (Fixed, 95% CI)	-1.53 [-1.95, -1.11]
6.1 (0.25 x starting dose) 1.0 & 1.25 mg/day	2	335	Mean Difference (Fixed, 95% CI)	-0.95 [-2.38, 0.48]

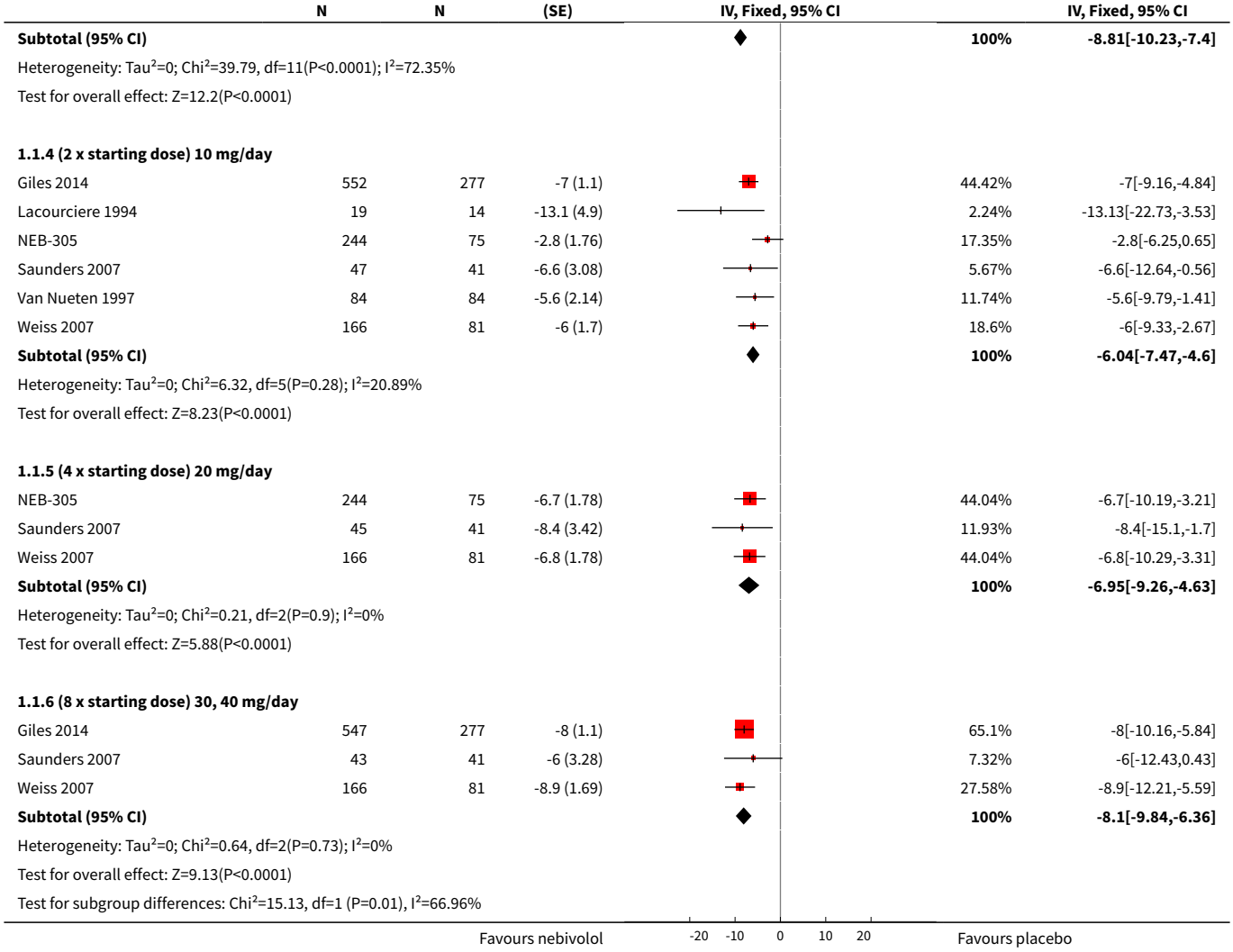
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2 (0.5 x starting dose) 2.5 mg/day	3	415	Mean Difference (Fixed, 95% CI)	-1.88 [-3.12, -0.64]
6.3 (starting dose) 5 mg/day	4	817	Mean Difference (Fixed, 95% CI)	-1.54 [-2.52, -0.57]
6.4 (2 x starting dose) 10 mg/day	4	822	Mean Difference (Fixed, 95% CI)	-1.06 [-1.86, -0.26]
6.5 (4 x starting dose) 20 mg/day	3	652	Mean Difference (Fixed, 95% CI)	-1.53 [-2.41, -0.65]
6.6 (8 x starting dose) 30, 40 mg/day	2	331	Mean Difference (Fixed, 95% CI)	-2.73 [-3.98, -1.49]

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

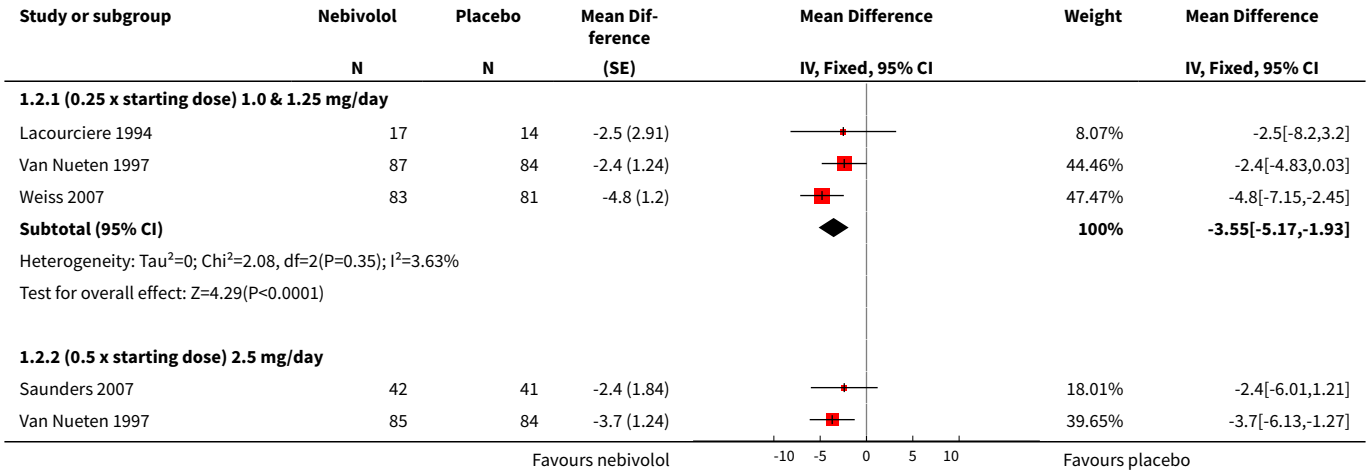
Study or subgroup	Nebivolol N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 (0.25 x starting dose) 1.0 & 1.25 mg/day						
Lacourciere 1994	17	14	-4.7 (5.02)		7.32%	-4.69[-14.53,5.15]
Van Nueten 1997	87	84	-6.2 (2.12)		41.04%	-6.2[-10.36,-2.04]
Weiss 2007	83	81	-3.1 (1.89)		51.64%	-3.1[-6.8,0.6]
Subtotal (95% CI)					**100%**	**-4.49[-7.15,-1.83]**
Heterogeneity: Tau^2=0; Chi^2=1.19, df=2(P=0.55); I^2=0%						
Test for overall effect: Z=3.3(P=0)						
1.1.2 (0.5 x starting dose) 2.5 mg/day						
Saunders 2007	42	41	-1 (3.41)		16.32%	-1[-7.68,5.68]
Van Nueten 1997	85	84	-7.2 (2.14)		41.45%	-7.2[-11.39,-3.01]
Weiss 2007	82	81	-4.3 (2.12)		42.23%	-4.3[-8.46,-0.14]
Subtotal (95% CI)					**100%**	**-4.96[-7.66,-2.26]**
Heterogeneity: Tau^2=0; Chi^2=2.54, df=2(P=0.28); I^2=21.3%						
Test for overall effect: Z=3.6(P=0)						
1.1.3 (starting dose) 5 mg/day						
Chan 1991	16	13	-20.5 (5.53)		1.71%	-20.5[-31.34,-9.66]
Chan 1992	18	14	-20.1 (4.83)		2.24%	-20.1[-29.57,-10.63]
Dhakam 2008	16	0	-13 (3)		5.8%	-13[-18.88,-7.12]
Himmelmann 1996	15	0	-12 (3.14)		5.29%	-12[-18.15,-5.85]
Lacourciere 1994	19	14	-11.2 (4.9)		2.17%	-11.25[-20.85,-1.65]
NEB-305	244	75	-4.2 (1.73)		17.43%	-4.2[-7.59,-0.81]
Saunders 2007	41	41	-2.3 (3.69)		3.83%	-2.3[-9.53,4.93]
Van Bortel 1993	80	0	-16 (2.38)		9.21%	-16[-20.66,-11.34]
Van Merode 1989	29	0	-10 (3)		5.8%	-10[-15.88,-4.12]
Van Nueten 1997	86	84	-6.9 (2.13)		11.5%	-6.9[-11.07,-2.73]
Van Nueten 1998	110	119	-11 (1.84)		15.41%	-11[-14.61,-7.39]
Weiss 2007	165	81	-5.2 (1.63)		19.63%	-5.2[-8.39,-2.01]

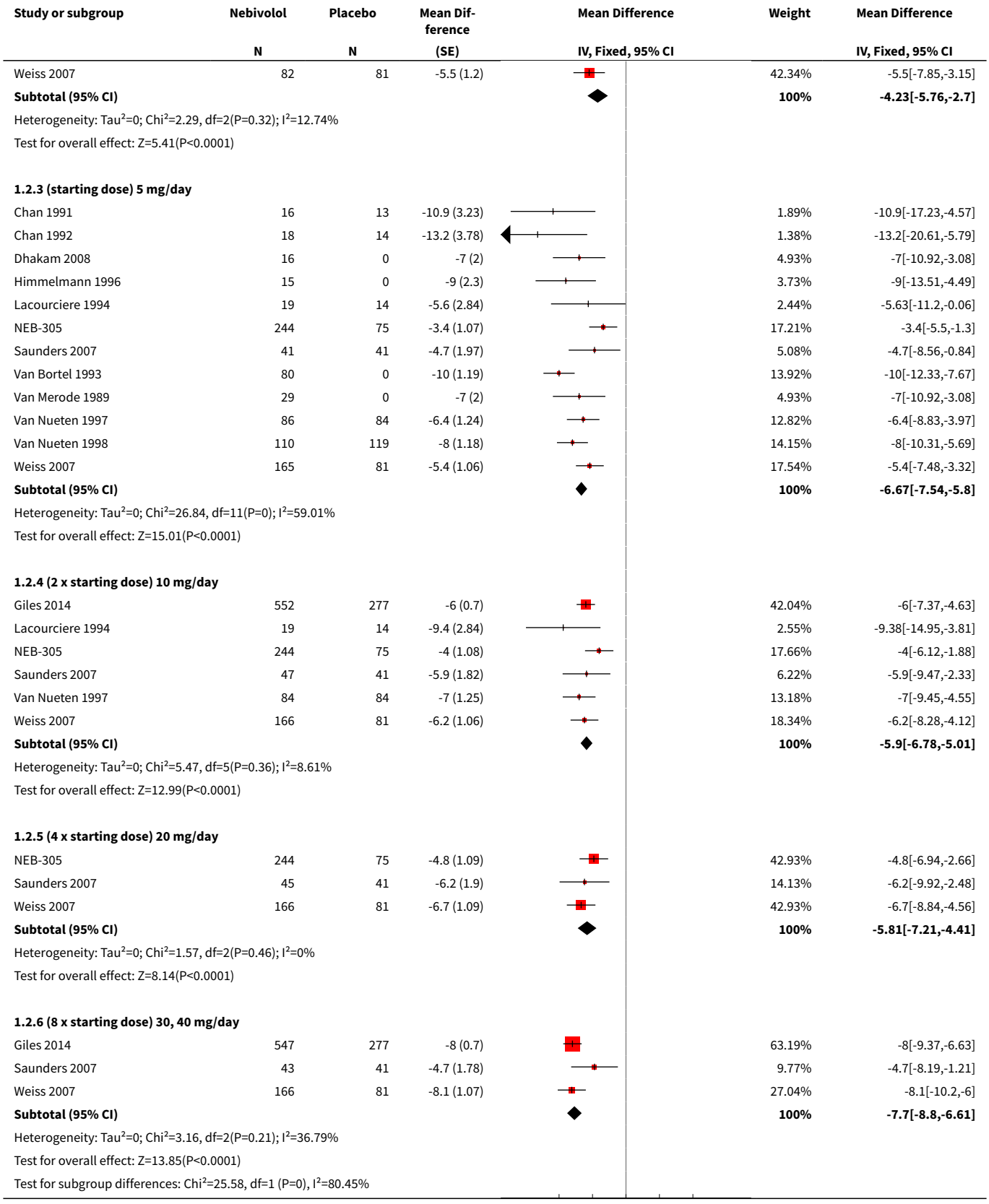


Favours nebivolol Favours placebo



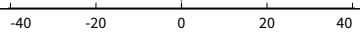
Analysis 1.2. Comparison 1 Nebivolol vs Placebo, Outcome 2 DBP.





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

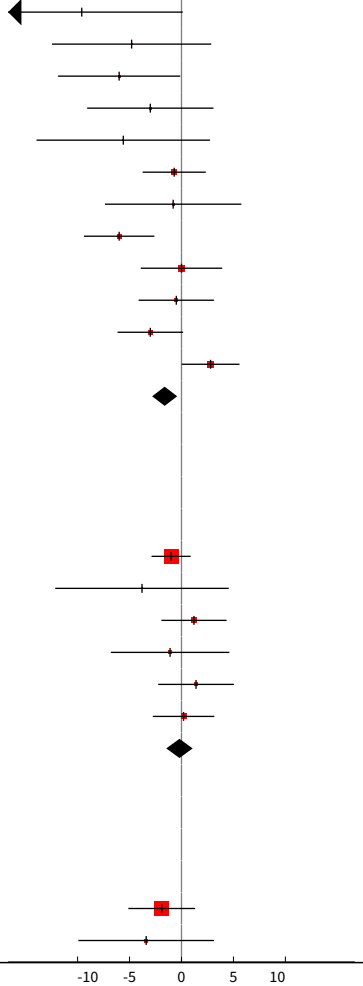
Study or subgroup	Nebivolol N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
1.3.1 (0.25 x starting dose) 1.25 mg/day						
Weiss 2007	69	67	-2.9 (1.51)		100%	-2.9[-5.86,0.06]
Subtotal (95% CI)					**100%**	**-2.9[-5.86,0.06]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.92(P=0.05)						
1.3.2 (0.5 x starting dose) 2.5 mg/day						
Saunders 2007	42	41	-2.8 (1.95)		35.61%	-2.8[-6.62,1.02]
Weiss 2007	68	67	-4.5 (1.45)		64.39%	-4.5[-7.34,-1.66]
Subtotal (95% CI)					**100%**	**-3.89[-6.18,-1.61]**
Heterogeneity: Tau^2=0; Chi^2=0.49, df=1(P=0.48); I^2=0%						
Test for overall effect: Z=3.35(P=0)						
1.3.3 (starting dose) 5 mg/day						
Chan 1991	16	13	-10.9 (3.23)		5.25%	-10.9[-17.23,-4.57]
Chan 1992	18	14	-1.5 (2.27)		10.64%	-1.5[-5.95,2.95]
Dhakam 2008	0	0	-19 (2.65)		7.81%	-19[-24.19,-13.81]
Himmelmann 1996	15	0	-6 (2.58)		8.24%	-6[-11.06,-0.94]
Saunders 2007	41	41	-2.3 (1.78)		17.3%	-2.3[-5.79,1.19]
Van Bortel 1993	114	0	-16 (1.73)		18.32%	-16[-19.39,-12.61]
Weiss 2007	148	67	-6.7 (1.3)		32.44%	-6.7[-9.25,-4.15]
Subtotal (95% CI)					**100%**	**-8.21[-9.66,-6.76]**
Heterogeneity: Tau^2=0; Chi^2=59.39, df=6(P<0.0001); I^2=89.9%						
Test for overall effect: Z=11.09(P<0.0001)						
1.3.4 (2 x starting dose) 10 mg/day						
Giles 2014	552	277	-8 (0.8)		62.81%	-8[-9.57,-6.43]
Saunders 2007	47	41	-4.4 (1.81)		12.27%	-4.4[-7.95,-0.85]
Weiss 2007	136	67	-6.7 (1.27)		24.92%	-6.7[-9.19,-4.21]
Subtotal (95% CI)					**100%**	**-7.23[-8.48,-5.99]**
Heterogeneity: Tau^2=0; Chi^2=3.55, df=2(P=0.17); I^2=43.59%						
Test for overall effect: Z=11.41(P<0.0001)						
1.3.5 (4 x starting dose) 20 mg/day						
Saunders 2007	45	41	-5.5 (1.81)		33.34%	-5.5[-9.05,-1.95]
Weiss 2007	145	67	-9.9 (1.28)		66.66%	-9.9[-12.41,-7.39]
Subtotal (95% CI)					**100%**	**-8.43[-10.48,-6.38]**
Heterogeneity: Tau^2=0; Chi^2=3.94, df=1(P=0.05); I^2=74.62%						
Test for overall effect: Z=8.07(P<0.0001)						
1.3.6 (8 x starting dose) 30, 40 mg/day						
Giles 2014	547	277	-12 (0.8)		62.36%	-12[-13.57,-10.43]
Saunders 2007	43	41	-7.2 (1.92)		10.83%	-7.2[-10.96,-3.44]
Weiss 2007	166	81	-10 (1.22)		26.81%	-10[-12.39,-7.61]
Subtotal (95% CI)					**100%**	**-10.94[-12.18,-9.71]**
Heterogeneity: Tau^2=0; Chi^2=6.14, df=2(P=0.05); I^2=67.45%						
Test for overall effect: Z=17.32(P<0.0001)						
Test for subgroup differences: Chi^2=47.18, df=1 (P<0.0001), I^2=89.4%						

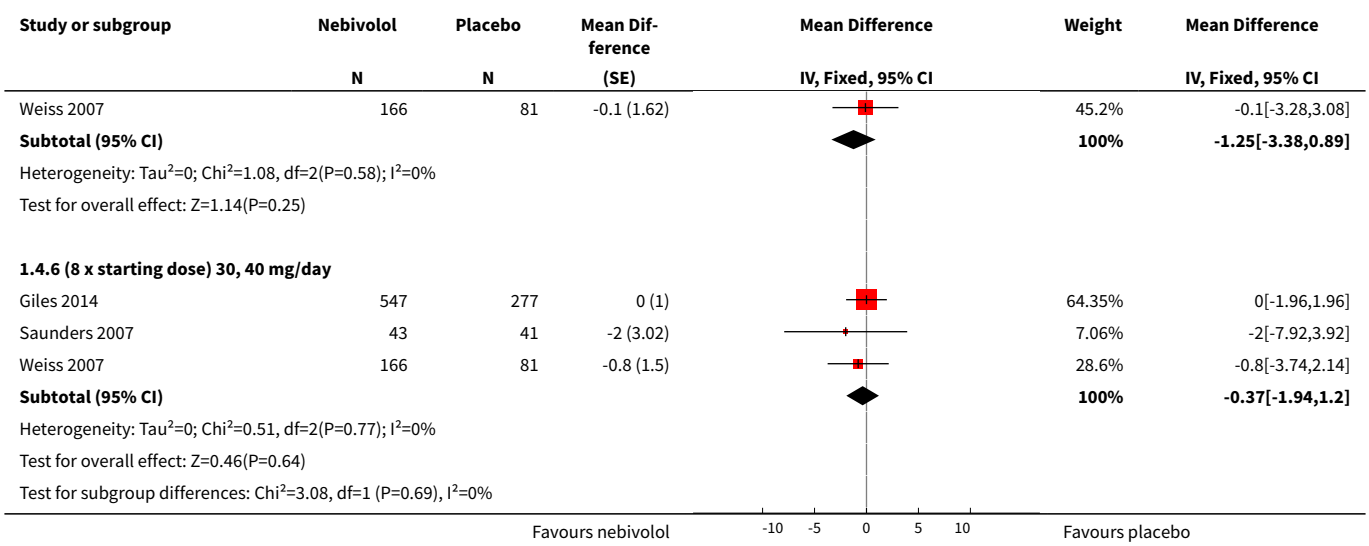


Favours nebivolol — Favours placebo

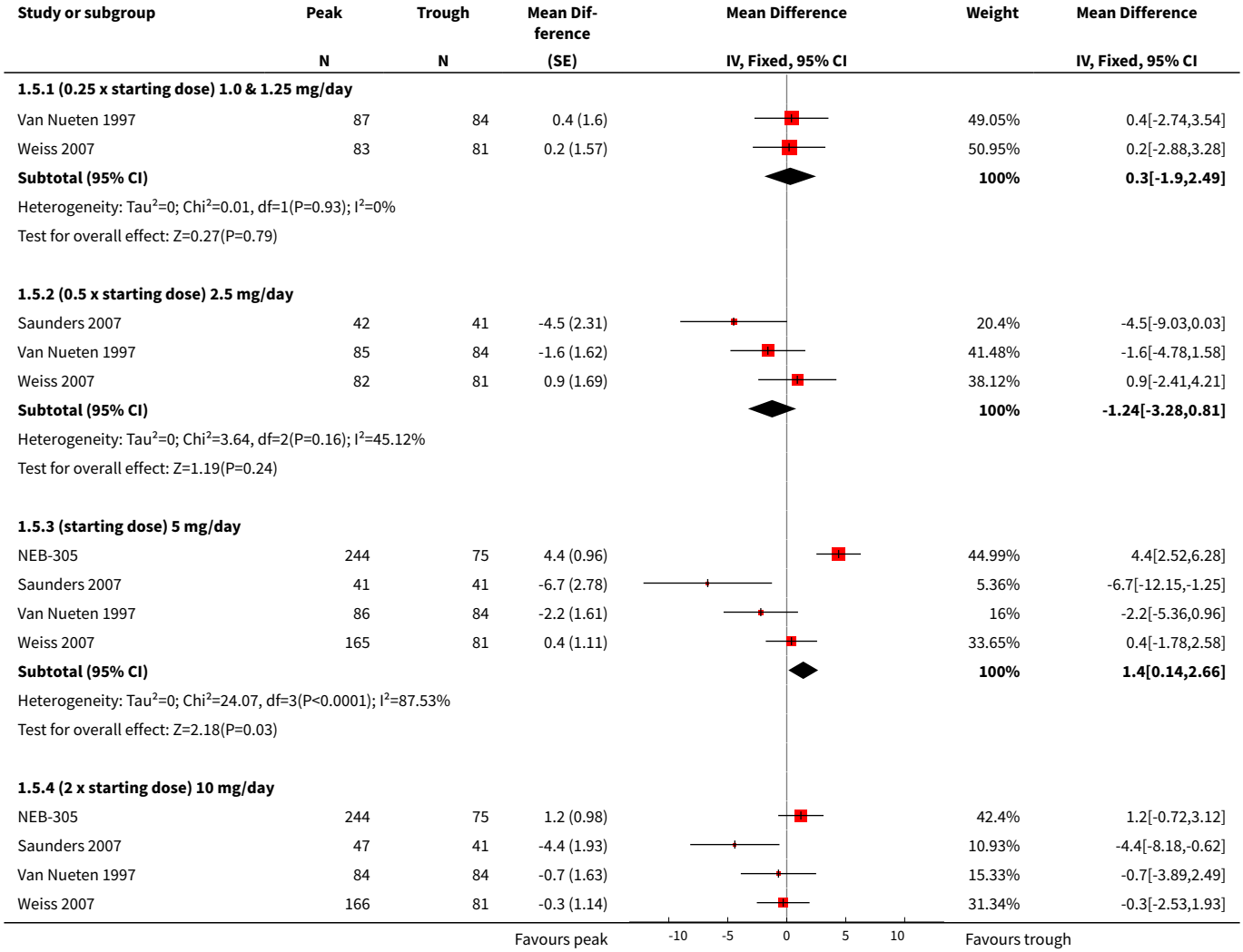
Analysis 1.4. Comparison 1 Nebivolol vs Placebo, Outcome 4 Pulse Pressure.

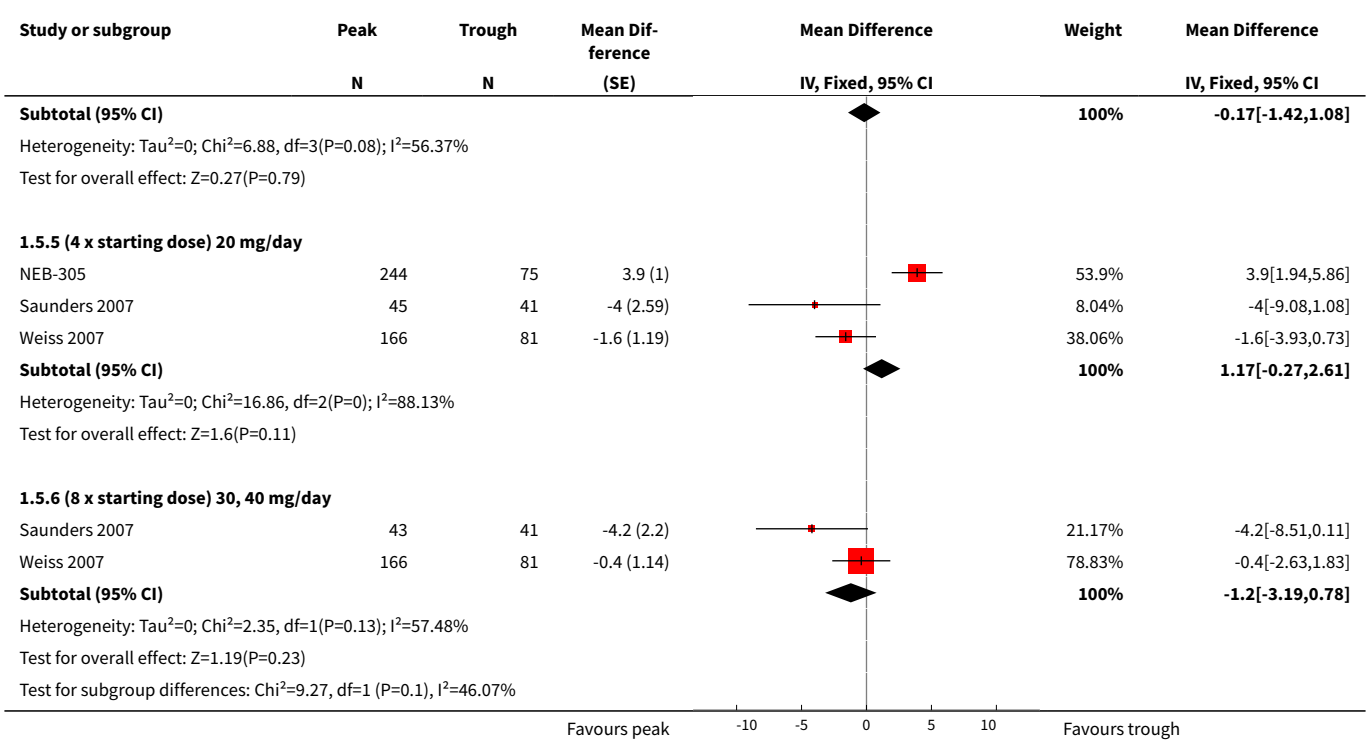
Study or subgroup	Nebivolol N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
1.4.1 (0.25 x starting dose) 1.0 & 1.25 mg/day						
Lacourciere 1994	17	14	-2.5 (4.36)		7.43%	-2.5[-11.05,6.05]
Van Nueten 1997	87	84	-3.8 (1.85)		41.29%	-3.8[-7.43,-0.17]
Weiss 2007	83	81	1.7 (1.66)		51.28%	1.7[-1.55,4.95]
Subtotal (95% CI)					**100%**	**-0.88[-3.21,1.45]**
Heterogeneity: Tau²=0; Chi²=5.04, df=2(P=0.08); I²=60.36%						
Test for overall effect: Z=0.74(P=0.46)						
1.4.2 (0.5 x starting dose) 2.5 mg/day						
Saunders 2007	42	41	0.1 (3.03)		15.85%	0.1[-5.84,6.04]
Van Nueten 1997	85	84	-3.5 (1.86)		42.07%	-3.5[-7.15,0.15]
Weiss 2007	82	81	1.2 (1.86)		42.07%	1.2[-2.45,4.85]
Subtotal (95% CI)					**100%**	**-0.95[-3.32,1.41]**
Heterogeneity: Tau²=0; Chi²=3.34, df=2(P=0.19); I²=40.04%						
Test for overall effect: Z=0.79(P=0.43)						
1.4.3 (starting dose) 5 mg/day						
Chan 1991	16	13	-9.6 (4.96)		1.54%	-9.6[-19.32,0.12]
Chan 1992	18	14	-4.8 (3.91)		2.48%	-4.8[-12.46,2.86]
Dhakam 2008	16	0	-6 (3)		4.21%	-6[-11.88,-0.12]
Himmelmann 1996	15	0	-3 (3.1)		3.94%	-3[-9.08,3.08]
Lacourciere 1994	19	14	-5.6 (4.26)		2.09%	-5.6[-13.95,2.75]
NEB-305	244	75	-0.7 (1.55)		15.77%	-0.7[-3.74,2.34]
Saunders 2007	41	41	-0.8 (3.35)		3.38%	-0.8[-7.37,5.77]
Van Bortel 1993	114	0	-6 (1.73)		12.66%	-6[-9.39,-2.61]
Van Merode 1989	29	0	0 (2)		9.47%	0[-3.92,3.92]
Van Nueten 1997	86	84	-0.5 (1.85)		11.07%	-0.5[-4.13,3.13]
Van Nueten 1998	110	119	-3 (1.61)		14.61%	-3[-6.16,0.16]
Weiss 2007	165	81	2.8 (1.42)		18.79%	2.8[0.02,5.58]
Subtotal (95% CI)					**100%**	**-1.62[-2.83,-0.41]**
Heterogeneity: Tau²=0; Chi²=24.72, df=11(P=0.01); I²=55.5%						
Test for overall effect: Z=2.63(P=0.01)						
1.4.4 (2 x starting dose) 10 mg/day						
Giles 2014	552	277	-1 (0.96)		45.66%	-1[-2.88,0.88]
Lacourciere 1994	19	14	-3.8 (4.26)		2.32%	-3.8[-12.15,4.55]
NEB-305	244	75	1.2 (1.6)		16.44%	1.2[-1.94,4.34]
Saunders 2007	47	41	-1.1 (2.91)		4.97%	-1.1[-6.8,4.6]
Van Nueten 1997	84	84	1.4 (1.86)		12.16%	1.4[-2.25,5.05]
Weiss 2007	166	81	0.2 (1.51)		18.45%	0.2[-2.76,3.16]
Subtotal (95% CI)					**100%**	**-0.19[-1.47,1.08]**
Heterogeneity: Tau²=0; Chi²=3.08, df=5(P=0.69); I²=0%						
Test for overall effect: Z=0.3(P=0.76)						
1.4.5 (4 x starting dose) 20 mg/day						
NEB-305	244	75	-1.9 (1.64)		44.1%	-1.9[-5.11,1.31]
Saunders 2007	45	41	-3.4 (3.33)		10.7%	-3.4[-9.93,3.13]



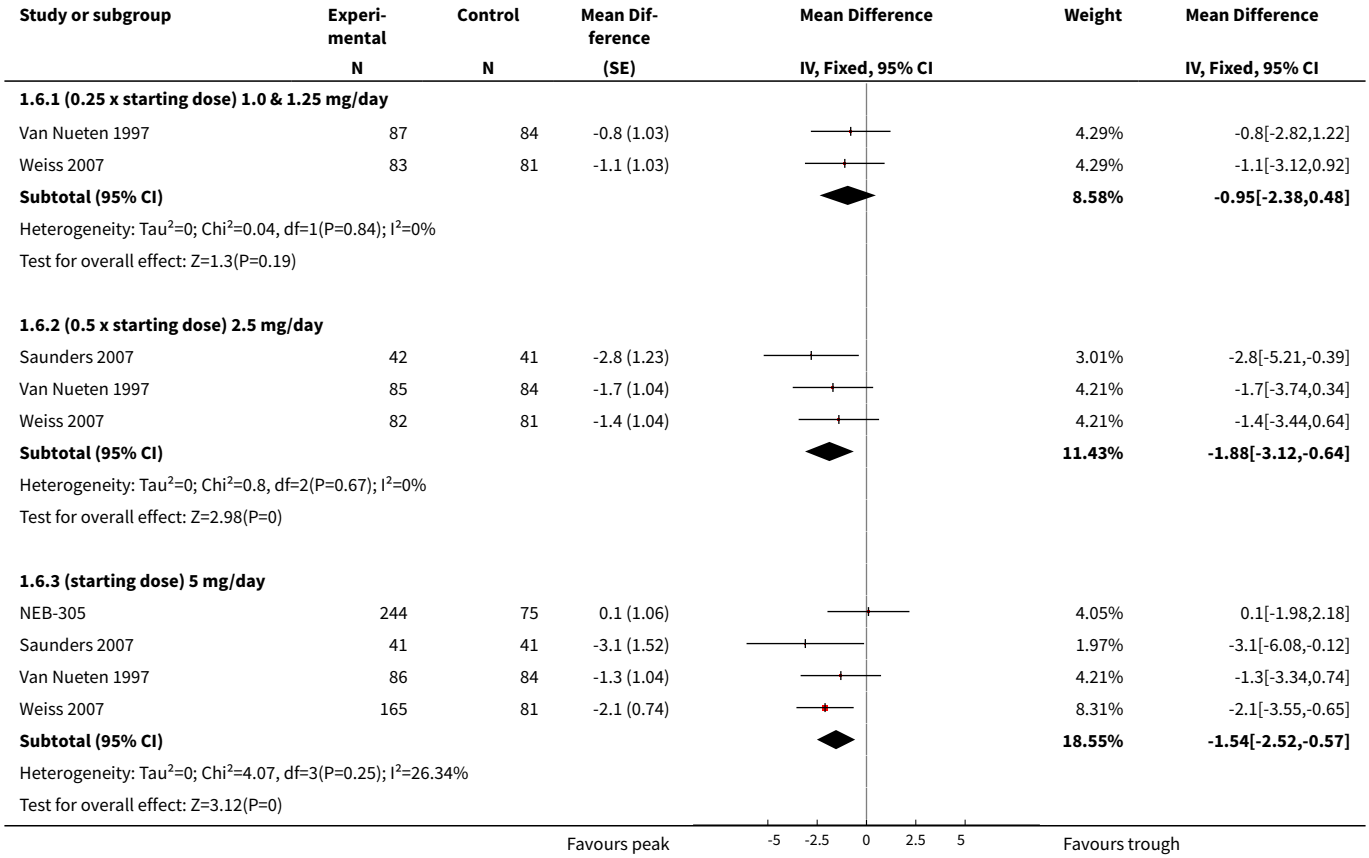


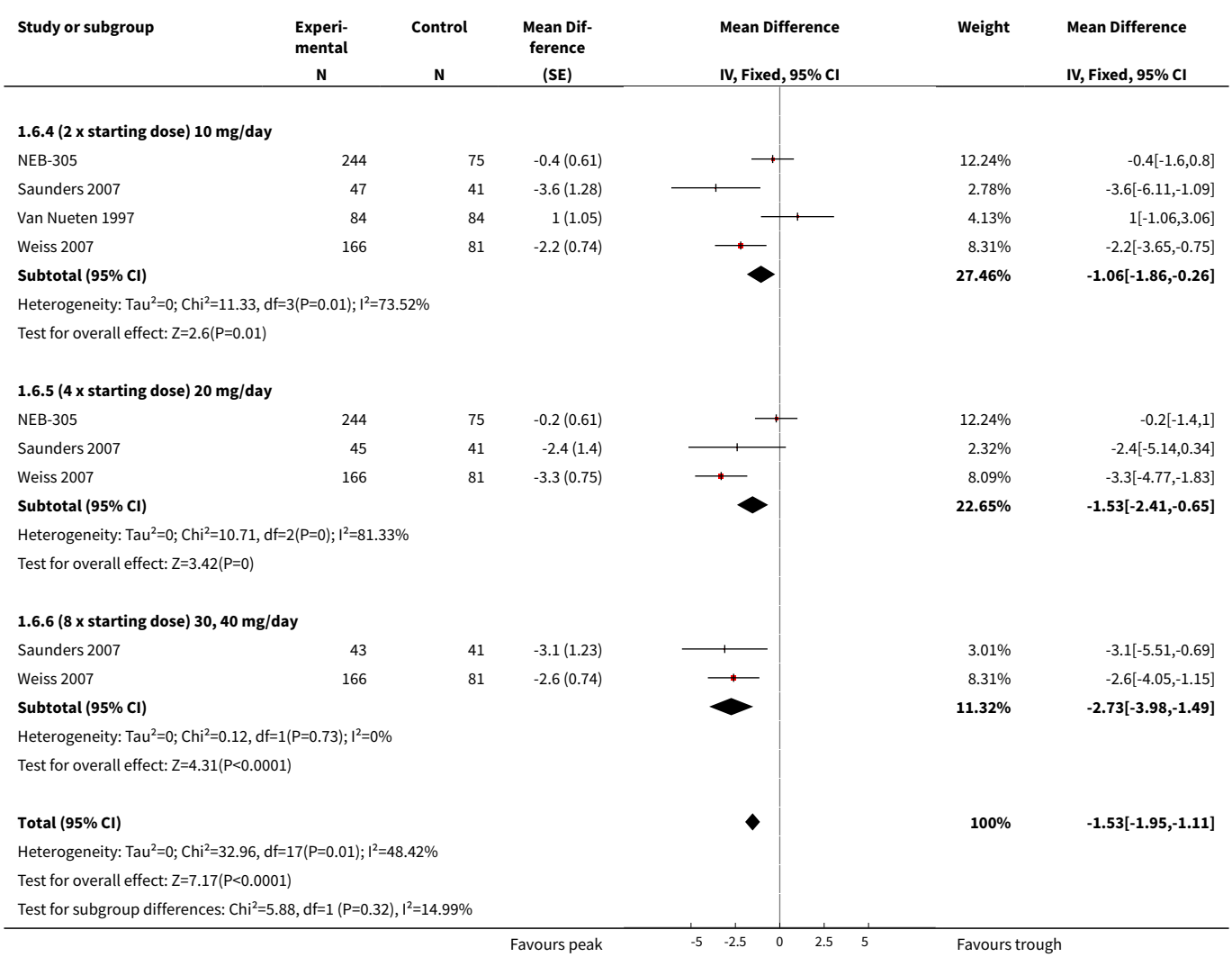
Analysis 1.5. Comparison 1 Nebivolol vs Placebo, Outcome 5 Peak vs Trough SBP.





Analysis 1.6. Comparison 1 Nebivolol vs Placebo, Outcome 6 Peak vs Trough DBP.





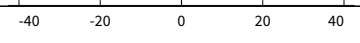
Comparison 2. Atenolol vs Placebo

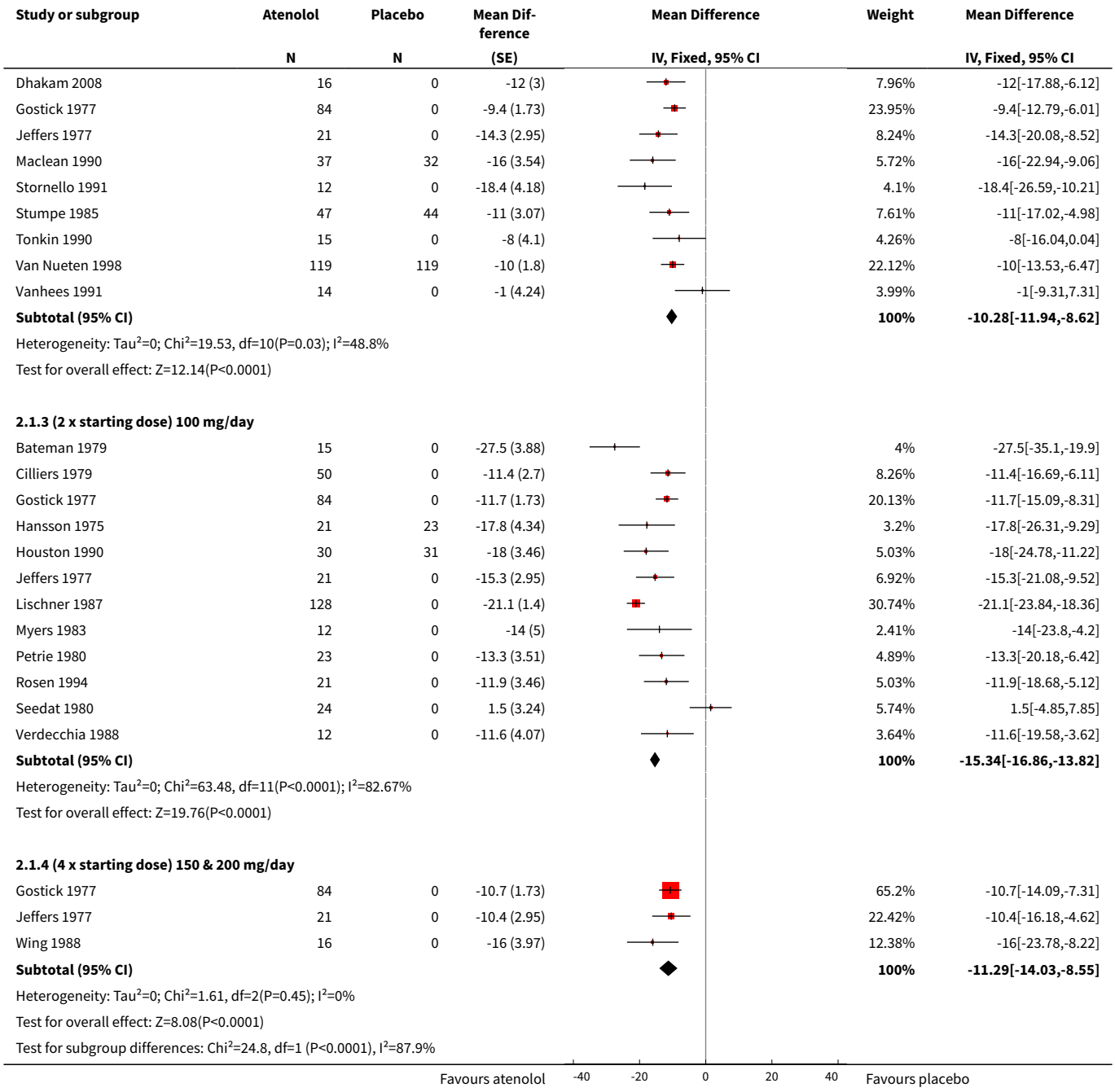
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SBP	22		Mean Difference (Fixed, 95% CI)	Subtotals only
1.1 (0.5 x starting dose) 25 mg/day	1	87	Mean Difference (Fixed, 95% CI)	-7.0 [-12.55, -1.45]
1.2 (starting dose) 50 mg/day	11	669	Mean Difference (Fixed, 95% CI)	-10.28 [-11.94, -8.62]
1.3 (2 x starting dose) 100 mg/day	12	495	Mean Difference (Fixed, 95% CI)	-15.34 [-16.86, -13.82]
1.4 (4 x starting dose) 150 & 200 mg/day	3	121	Mean Difference (Fixed, 95% CI)	-11.29 [-14.03, -8.55]
2 DBP	22		Mean Difference (Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 (0.5 x starting dose) 25 mg/day	1	87	Mean Difference (Fixed, 95% CI)	-4.0 [-6.76, -1.24]
2.2 (starting dose) 50 mg/day	11	657	Mean Difference (Fixed, 95% CI)	-7.78 [-8.80, -6.76]
2.3 (2 x starting dose) 100 mg/day	12	495	Mean Difference (Fixed, 95% CI)	-12.91 [-13.89, -11.93]
2.4 (4 x starting dose) 150, 200 mg/day	3	121	Mean Difference (Fixed, 95% CI)	-8.76 [-10.56, -6.95]
3 Heart rate	17		Mean Difference (Fixed, 95% CI)	Subtotals only
3.1 (0.5 x starting dose) 25 mg/day	1	87	Mean Difference (Fixed, 95% CI)	-4.0 [-9.55, 1.55]
3.2 (starting dose) 50 mg/day	7	470	Mean Difference (Fixed, 95% CI)	-12.04 [-13.39, -10.68]
3.3 (2 x starting dose) 100 mg/day	10	413	Mean Difference (Fixed, 95% CI)	-13.70 [-14.83, -12.56]
3.4 (4 x starting dose) 150, 200 mg/day	4	129	Mean Difference (Fixed, 95% CI)	-18.33 [-20.26, -16.41]
4 Pulse pressure	22		Mean Difference (Fixed, 95% CI)	Subtotals only
4.1 (0.5 x starting dose) 25 mg/day	1	87	Mean Difference (Fixed, 95% CI)	-3.0 [-7.80, 1.80]
4.2 (starting dose) 50 mg/day	11	669	Mean Difference (Fixed, 95% CI)	-2.30 [-3.71, -0.90]
4.3 (2 x starting dose) 100 mg/day	12	495	Mean Difference (Fixed, 95% CI)	-2.01 [-3.24, -0.77]
4.4 (4 x starting dose) 150, 200 mg/day	3	121	Mean Difference (Fixed, 95% CI)	-2.62 [-4.82, -0.42]

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

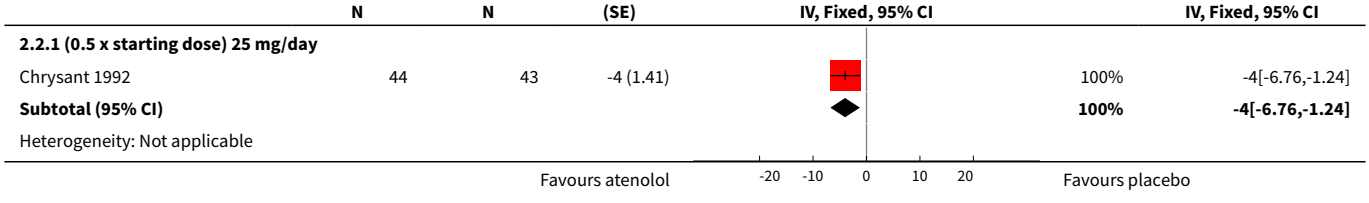
Study or subgroup	Atenolol N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
2.1.1 (0.5 x starting dose) 25 mg/day						
Chrysant 1992	44	43	-7 (2.83)		100%	-7[-12.55,-1.45]
Subtotal (95% CI)					**100%**	**-7[-12.55,-1.45]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.47(P=0.01)						
2.1.2 (starting dose) 50 mg/day						
Baez 1986	12	12	-14 (4.81)		3.1%	-14[-23.43,-4.57]
Chrysant 1992	42	43	-4 (2.83)		8.95%	-4[-9.55,1.55]





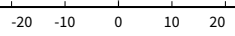
Study or subgroup	Atenolol N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Dhakam 2008	16	0	-12 (3)		7.96%	-12[-17.88,-6.12]
Gostick 1977	84	0	-9.4 (1.73)		23.95%	-9.4[-12.79,-6.01]
Jeffers 1977	21	0	-14.3 (2.95)		8.24%	-14.3[-20.08,-8.52]
Maclean 1990	37	32	-16 (3.54)		5.72%	-16[-22.94,-9.06]
Stornello 1991	12	0	-18.4 (4.18)		4.1%	-18.4[-26.59,-10.21]
Stumpe 1985	47	44	-11 (3.07)		7.61%	-11[-17.02,-4.98]
Tonkin 1990	15	0	-8 (4.1)		4.26%	-8[-16.04,0.04]
Van Nueten 1998	119	119	-10 (1.8)		22.12%	-10[-13.53,-6.47]
Vanhees 1991	14	0	-1 (4.24)		3.99%	-1[-9.31,7.31]
Subtotal (95% CI)					**100%**	**-10.28[-11.94,-8.62]**
Heterogeneity: Tau²=0; Chi²=19.53, df=10(P=0.03); I²=48.8%						
Test for overall effect: Z=12.14(P<0.0001)						
2.1.3 (2 x starting dose) 100 mg/day						
Bateman 1979	15	0	-27.5 (3.88)		4%	-27.5[-35.1,-19.9]
Cilliers 1979	50	0	-11.4 (2.7)		8.26%	-11.4[-16.69,-6.11]
Gostick 1977	84	0	-11.7 (1.73)		20.13%	-11.7[-15.09,-8.31]
Hansson 1975	21	23	-17.8 (4.34)		3.2%	-17.8[-26.31,-9.29]
Houston 1990	30	31	-18 (3.46)		5.03%	-18[-24.78,-11.22]
Jeffers 1977	21	0	-15.3 (2.95)		6.92%	-15.3[-21.08,-9.52]
Lischner 1987	128	0	-21.1 (1.4)		30.74%	-21.1[-23.84,-18.36]
Myers 1983	12	0	-14 (5)		2.41%	-14[-23.8,-4.2]
Petrie 1980	23	0	-13.3 (3.51)		4.89%	-13.3[-20.18,-6.42]
Rosen 1994	21	0	-11.9 (3.46)		5.03%	-11.9[-18.68,-5.12]
Seedat 1980	24	0	1.5 (3.24)		5.74%	1.5[-4.85,7.85]
Verdecchia 1988	12	0	-11.6 (4.07)		3.64%	-11.6[-19.58,-3.62]
Subtotal (95% CI)					**100%**	**-15.34[-16.86,-13.82]**
Heterogeneity: Tau²=0; Chi²=63.48, df=11(P<0.0001); I²=82.67%						
Test for overall effect: Z=19.76(P<0.0001)						
2.1.4 (4 x starting dose) 150 & 200 mg/day						
Gostick 1977	84	0	-10.7 (1.73)		65.2%	-10.7[-14.09,-7.31]
Jeffers 1977	21	0	-10.4 (2.95)		22.42%	-10.4[-16.18,-4.62]
Wing 1988	16	0	-16 (3.97)		12.38%	-16[-23.78,-8.22]
Subtotal (95% CI)					**100%**	**-11.29[-14.03,-8.55]**
Heterogeneity: Tau²=0; Chi²=1.61, df=2(P=0.45); I²=0%						
Test for overall effect: Z=8.08(P<0.0001)						
Test for subgroup differences: Chi²=24.8, df=1 (P<0.0001), I²=87.9%						

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



Study or subgroup	Atenolol N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
2.2.1 (0.5 x starting dose) 25 mg/day						
Chrysant 1992	44	43	-4 (1.41)		100%	-4[-6.76,-1.24]
Subtotal (95% CI)					**100%**	**-4[-6.76,-1.24]**
Heterogeneity: Not applicable						

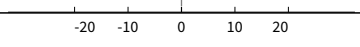
Study or subgroup	Atenolol N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Test for overall effect: Z=2.84(P=0)						
2.2.2 (starting dose) 50 mg/day						
Baez 1986	12	12	-6 (3.47)		2.27%	-6[-12.8,0.8]
Chrysant 1992	42	43	-5 (1.54)		11.5%	-5[-8.02,-1.98]
Dhakam 2008	16	0	-9 (2)		6.82%	-9[-12.92,-5.08]
Gostick 1977	84	0	-7.2 (1.14)		20.99%	-7.2[-9.43,-4.97]
Jeffers 1977	21	0	-11.5 (1.95)		7.17%	-11.5[-15.32,-7.68]
Maclean 1990	37	32	-13 (1.71)		9.33%	-13[-16.35,-9.65]
Stornello 1991	0	0	-15.6 (2.76)		3.58%	-15.6[-21.01,-10.19]
Stumpe 1985	47	44	-4 (1.49)		12.29%	-4[-6.92,-1.08]
Tonkin 1990	15	0	-9 (3.02)		2.99%	-9[-14.92,-3.08]
Van Nueten 1998	119	119	-7 (1.18)		19.59%	-7[-9.31,-4.69]
Vanhees 1991	14	0	-6.2 (2.8)		3.48%	-6.25[-11.74,-0.76]
Subtotal (95% CI)					**100%**	**-7.78[-8.8,-6.76]**
Heterogeneity: Tau^2=0; Chi^2=32.47, df=10(P=0); I^2=69.21%						
Test for overall effect: Z=14.9(P<0.0001)						
2.2.3 (2 x starting dose) 100 mg/day						
Bateman 1979	15	0	-19.2 (2.57)		3.8%	-19.2[-24.24,-14.16]
Cilliers 1979	50	0	-10.3 (1.78)		7.92%	-10.3[-13.79,-6.81]
Gostick 1977	84	0	-8.9 (1.14)		19.3%	-8.9[-11.13,-6.67]
Hansson 1975	21	23	-11.3 (3.04)		2.71%	-11.3[-17.26,-5.34]
Houston 1990	30	31	-8 (1.67)		8.99%	-8[-11.27,-4.73]
Jeffers 1977	21	0	-14.5 (1.95)		6.6%	-14.5[-18.32,-10.68]
Lischner 1987	128	0	-19.4 (0.92)		29.63%	-19.4[-21.2,-17.6]
Myers 1983	12	0	-18 (3)		2.79%	-18[-23.88,-12.12]
Petrie 1980	23	0	-9.2 (2.43)		4.25%	-9.2[-13.96,-4.44]
Rosen 1994	21	0	-8.9 (2.28)		4.83%	-8.88[-13.35,-4.41]
Seedat 1980	24	0	-4.2 (2.14)		5.48%	-4.2[-8.39,-0.01]
Verdecchia 1988	12	0	-9.8 (2.6)		3.71%	-9.8[-14.9,-4.7]
Subtotal (95% CI)					**100%**	**-12.91[-13.89,-11.93]**
Heterogeneity: Tau^2=0; Chi^2=106.2, df=11(P<0.0001); I^2=89.64%						
Test for overall effect: Z=25.77(P<0.0001)						
2.2.4 (4 x starting dose) 150, 200 mg/day						
Gostick 1977	84	0	-7.6 (1.14)		65.31%	-7.6[-9.83,-5.37]
Jeffers 1977	21	0	-9.8 (1.95)		22.32%	-9.8[-13.62,-5.98]
Wing 1988	16	0	-13 (2.62)		12.37%	-13[-18.14,-7.86]
Subtotal (95% CI)					**100%**	**-8.76[-10.56,-6.95]**
Heterogeneity: Tau^2=0; Chi^2=3.94, df=2(P=0.14); I^2=49.22%						
Test for overall effect: Z=9.51(P<0.0001)						
Test for subgroup differences: Chi^2=71.59, df=1 (P<0.0001), I^2=95.81%						



Favours atenolol Favours placebo

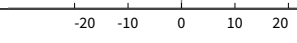
Analysis 2.3. Comparison 2 Atenolol vs Placebo, Outcome 3 Heart rate.

Study or subgroup	Atenolol N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
2.3.1 (0.5 x starting dose) 25 mg/day						
Chrysant 1992	44	43	-4 (2.83)		100%	-4[-9.55,1.55]
Subtotal (95% CI)					**100%**	**-4[-9.55,1.55]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.41(P=0.16)						
2.3.2 (starting dose) 50 mg/day						
Chrysant 1992	42	43	-3 (2.83)		5.98%	-3[-8.55,2.55]
Dhakam 2008	16	0	-23 (2.87)		5.81%	-23[-28.63,-17.37]
Gostick 1977	84	0	-13.8 (1.4)		24.42%	-13.8[-16.54,-11.06]
Jeffers 1977	21	0	-17.8 (1.8)		14.77%	-17.8[-21.33,-14.27]
Stornello 1991	12	0	-10.6 (2.75)		6.33%	-10.6[-15.99,-5.21]
Van Nueten 1998	119	119	-7.7 (1.17)		34.97%	-7.7[-9.99,-5.41]
Vanhees 1991	14	0	-15 (2.49)		7.72%	-15[-19.88,-10.12]
Subtotal (95% CI)					**100%**	**-12.04[-13.39,-10.68]**
Heterogeneity: Tau^2=0; Chi^2=52.05, df=6(P<0.0001); I^2=88.47%						
Test for overall effect: Z=17.4(P<0.0001)						
2.3.3 (2 x starting dose) 100 mg/day						
Bateman 1979	15	0	-28.6 (2.96)		3.82%	-28.6[-34.4,-22.8]
Cilliers 1979	50	0	-12.4 (1.62)		12.75%	-12.45[-15.63,-9.27]
Gostick 1977	84	0	-15.6 (1.35)		18.36%	-15.6[-18.25,-12.95]
Hansson 1975	21	23	-15.7 (3.33)		3.02%	-15.7[-22.23,-9.17]
Jeffers 1977	21	0	-24.8 (1.8)		10.33%	-24.8[-28.33,-21.27]
Lischner 1987	128	0	-8.3 (1.01)		32.81%	-8.3[-10.28,-6.32]
Myers 1983	12	0	-24 (3.3)		3.07%	-24[-30.47,-17.53]
Petrie 1980	23	0	-5.9 (2.39)		5.86%	-5.9[-10.58,-1.22]
Seedat 1980	24	0	-12.3 (2.2)		6.92%	-12.3[-16.61,-7.99]
Verdecchia 1988	12	0	-15 (3.31)		3.05%	-15[-21.49,-8.51]
Subtotal (95% CI)					**100%**	**-13.7[-14.83,-12.56]**
Heterogeneity: Tau^2=0; Chi^2=115.84, df=9(P<0.0001); I^2=92.23%						
Test for overall effect: Z=23.67(P<0.0001)						
2.3.4 (4 x starting dose) 150, 200 mg/day						
Frisk-Holmberg 1985	8	0	-15 (4.05)		5.86%	-15[-22.94,-7.06]
Gostick 1977	84	0	-15.1 (1.35)		52.77%	-15.1[-17.75,-12.45]
Jeffers 1977	21	0	-23.3 (1.8)		29.69%	-23.3[-26.83,-19.77]
Wing 1988	16	0	-22 (2.87)		11.68%	-22[-27.63,-16.37]
Subtotal (95% CI)					**100%**	**-18.33[-20.26,-16.41]**
Heterogeneity: Tau^2=0; Chi^2=15.66, df=3(P=0); I^2=80.84%						
Test for overall effect: Z=18.69(P<0.0001)						
Test for subgroup differences: Chi^2=39.85, df=1 (P<0.0001), I^2=92.47%						



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

Study or subgroup	Atenolol N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
2.4.1 (0.5 x starting dose) 25 mg/day						
Chrysant 1992	44	43	-3 (2.45)		100%	-3[-7.8,1.8]
Subtotal (95% CI)					**100%**	**-3[-7.8,1.8]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.22(P=0.22)						
2.4.2 (starting dose) 50 mg/day						
Baez 1986	12	12	-10 (4.45)		2.59%	-10[-18.72,-1.28]
Chrysant 1992	42	43	1 (2.45)		8.53%	1[-3.8,5.8]
Dhakam 2008	16	0	-3 (2.65)		7.29%	-3[-8.19,2.19]
Gostick 1977	84	0	-2.2 (1.36)		27.69%	-2.2[-4.87,0.47]
Jeffers 1977	21	0	-2.8 (2.6)		7.58%	-2.8[-7.9,2.3]
Maclean 1990	37	32	-3 (3.06)		5.47%	-3[-9,3]
Stornello 1991	12	0	-2.8 (3.68)		3.78%	-2.8[-10.01,4.41]
Stumpe 1985	47	44	-7 (2.66)		7.24%	-7[-12.21,-1.79]
Tonkin 1990	15	0	1 (3.22)		4.94%	1[-5.31,7.31]
Van Nueten 1998	119	119	-3 (1.59)		20.26%	-3[-6.12,0.12]
Vanhees 1991	14	0	5.3 (3.33)		4.62%	5.3[-1.23,11.83]
Subtotal (95% CI)					**100%**	**-2.3[-3.71,-0.9]**
Heterogeneity: Tau^2=0; Chi^2=14.57, df=10(P=0.15); I^2=31.35%						
Test for overall effect: Z=3.22(P=0)						
2.4.3 (2 x starting dose) 100 mg/day						
Bateman 1979	15	0	-8.3 (3.42)		3.39%	-8.3[-15,-1.6]
Cilliers 1979	50	0	-1.1 (2.38)		7.01%	-1.1[-5.76,3.56]
Gostick 1977	84	0	-2.8 (1.36)		21.47%	-2.8[-5.47,-0.13]
Hansson 1975	21	23	-6.5 (3.86)		2.66%	-6.5[-14.07,1.07]
Houston 1990	30	31	-10 (3)		4.41%	-10[-15.88,-4.12]
Jeffers 1977	21	0	-0.8 (2.6)		5.87%	-0.8[-5.9,4.3]
Lischner 1987	128	0	-1.7 (1.1)		32.81%	-1.7[-3.86,0.46]
Myers 1983	12	0	4 (4.63)		1.85%	4[-5.07,13.07]
Petrie 1980	23	0	-4.1 (2.6)		5.87%	-4.1[-9.2,1]
Rosen 1994	21	0	0.8 (2.72)		5.37%	0.8[-4.53,6.13]
Seedat 1980	24	0	5.7 (2.54)		6.15%	5.7[0.72,10.68]
Verdecchia 1988	12	0	-1.8 (3.57)		3.12%	-1.8[-8.8,5.2]
Subtotal (95% CI)					**100%**	**-2.01[-3.24,-0.77]**
Heterogeneity: Tau^2=0; Chi^2=25.22, df=11(P=0.01); I^2=56.39%						
Test for overall effect: Z=3.19(P=0)						
2.4.4 (4 x starting dose) 150, 200 mg/day						
Gostick 1977	84	0	-3.1 (1.36)		68.32%	-3.1[-5.77,-0.43]
Jeffers 1977	21	0	-0.6 (2.6)		18.69%	-0.6[-5.7,4.5]
Wing 1988	16	0	-3 (3.12)		12.98%	-3[-9.12,3.12]
Subtotal (95% CI)					**100%**	**-2.62[-4.82,-0.42]**
Heterogeneity: Tau^2=0; Chi^2=0.74, df=2(P=0.69); I^2=0%						
Test for overall effect: Z=2.33(P=0.02)						
Test for subgroup differences: Chi^2=0.35, df=1 (P=0.95), I^2=0%						



Favours atenolol Favours placebo

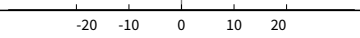
Comparison 3. Metoprolol vs Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SBP	9		Mean Difference (Fixed, 95% CI)	Subtotals only
1.1 (0.25 x starting dose) 25 mg/day	2	424	Mean Difference (Fixed, 95% CI)	-6.33 [-9.22, -3.44]
1.2 (0.5 x starting dose) 50 mg/day	2	339	Mean Difference (Fixed, 95% CI)	-6.30 [-9.47, -3.13]
1.3 (starting dose) 100 mg/day	3	410	Mean Difference (Fixed, 95% CI)	-5.35 [-8.12, -2.58]
1.4 (2 x starting dose) 200 mg/day	5	284	Mean Difference (Fixed, 95% CI)	-11.54 [-14.37, -8.71]
1.5 (4 x starting dose) 400 mg/day	2	193	Mean Difference (Fixed, 95% CI)	-10.91 [-15.42, -6.40]
2 DBP	9		Mean Difference (Fixed, 95% CI)	Subtotals only
2.1 (0.25 x starting dose) 25 mg/day	2	424	Mean Difference (Fixed, 95% CI)	-3.64 [-5.44, -1.85]
2.2 (0.5 x starting dose) 50 mg/day	2	339	Mean Difference (Fixed, 95% CI)	-4.56 [-6.42, -2.70]
2.3 (starting dose) 100 & 120 mg/day	3	410	Mean Difference (Fixed, 95% CI)	-4.74 [-6.50, -2.98]
2.4 (2 x starting dose) 200 mg/day	5	284	Mean Difference (Fixed, 95% CI)	-10.25 [-11.99, -8.51]
2.5 (4 x starting dose) 400 mg/day	2	193	Mean Difference (Fixed, 95% CI)	-7.71 [-10.72, -4.69]
3 Heart rate	5		Mean Difference (Fixed, 95% CI)	Subtotals only
3.1 (0.5 x starting dose) 50 mg/day	1	94	Mean Difference (Fixed, 95% CI)	-5.6 [-10.03, -1.17]
3.2 (starting dose) 100 & 120 mg/day	1	24	Mean Difference (Fixed, 95% CI)	-15.0 [-18.92, -11.08]
3.3 (2 x starting dose) 200 mg/day	2	40	Mean Difference (Fixed, 95% CI)	-13.25 [-17.04, -9.46]
3.4 (4 x starting dose) 400 mg/day	1	8	Mean Difference (Fixed, 95% CI)	-20.00 [-25.88, -14.12]
4 Pulse pressure	9		Mean Difference (Fixed, 95% CI)	Subtotals only
4.1 (0.25 x starting dose) 25 mg/day	2	424	Mean Difference (Fixed, 95% CI)	-2.70 [-5.23, -0.17]

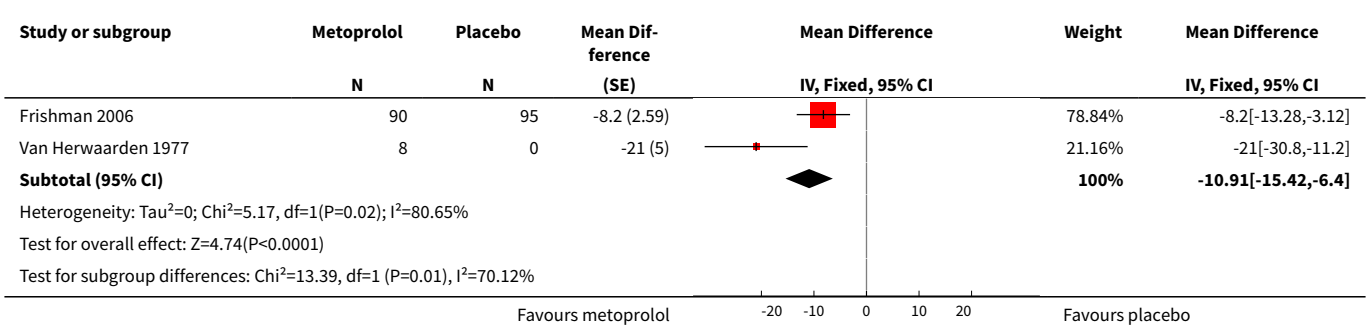
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 (0.5 x starting dose) 50 mg/day	2	339	Mean Difference (Fixed, 95% CI)	-1.74 [-4.52, 1.04]
4.3 (starting dose) 100 mg/day	3	410	Mean Difference (Fixed, 95% CI)	-0.58 [-3.01, 1.85]
4.4 (2 x starting dose) 200 mg/day	5	284	Mean Difference (Fixed, 95% CI)	-1.22 [-3.62, 1.18]
4.5 (4 x starting dose) 400 mg/day	2	193	Mean Difference (Fixed, 95% CI)	-3.30 [-7.29, 0.69]

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

Study or subgroup	Metoprolol N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
3.1.1 (0.25 x starting dose) 25 mg/day						
Frishman 2006	88	95	-6.3 (2.54)		33.68%	-6.3[-11.28,-1.32]
Papademetriou 2006	89	152	-6.3 (1.81)		66.32%	-6.35[-9.9,-2.8]
Subtotal (95% CI)					**100%**	**-6.33[-9.22,-3.44]**
Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.99); I²=0%						
Test for overall effect: Z=4.3(P<0.0001)						
3.1.2 (0.5 x starting dose) 50 mg/day						
Jaattela 1990	49	45	-4.9 (3.88)		17.39%	-4.88[-12.48,2.72]
Papademetriou 2006	93	152	-6.6 (1.78)		82.61%	-6.6[-10.09,-3.11]
Subtotal (95% CI)					**100%**	**-6.3[-9.47,-3.13]**
Heterogeneity: Tau²=0; Chi²=0.16, df=1(P=0.69); I²=0%						
Test for overall effect: Z=3.89(P<0.0001)						
3.1.3 (starting dose) 100 mg/day						
Bengtsson 1976	24	0	-8 (3.86)		13.41%	-8[-15.57,-0.43]
Frishman 2006	44	95	-2.4 (2.96)		22.81%	-2.4[-8.2,3.4]
Papademetriou 2006	95	152	-5.8 (1.77)		63.78%	-5.85[-9.32,-2.38]
Subtotal (95% CI)					**100%**	**-5.35[-8.12,-2.58]**
Heterogeneity: Tau²=0; Chi²=1.54, df=2(P=0.46); I²=0%						
Test for overall effect: Z=3.79(P=0)						
3.1.4 (2 x starting dose) 200 mg/day						
Ades 1990	10	10	-11 (6.92)		4.35%	-11[-24.56,2.56]
Gudbjornsdottir 1997	7	0	-22 (5.84)		6.11%	-22[-33.45,-10.55]
Lepantalo 1983	34	0	-8.9 (2.68)		29%	-8.9[-14.15,-3.65]
Papademetriou 2006	51	152	-10.2 (2.19)		43.43%	-10.25[-14.54,-5.96]
Verdecchia 1983	20	0	-15.7 (3.49)		17.1%	-15.7[-22.54,-8.86]
Subtotal (95% CI)					**100%**	**-11.54[-14.37,-8.71]**
Heterogeneity: Tau²=0; Chi²=5.95, df=4(P=0.2); I²=32.8%						
Test for overall effect: Z=8(P<0.0001)						
3.1.5 (4 x starting dose) 400 mg/day						

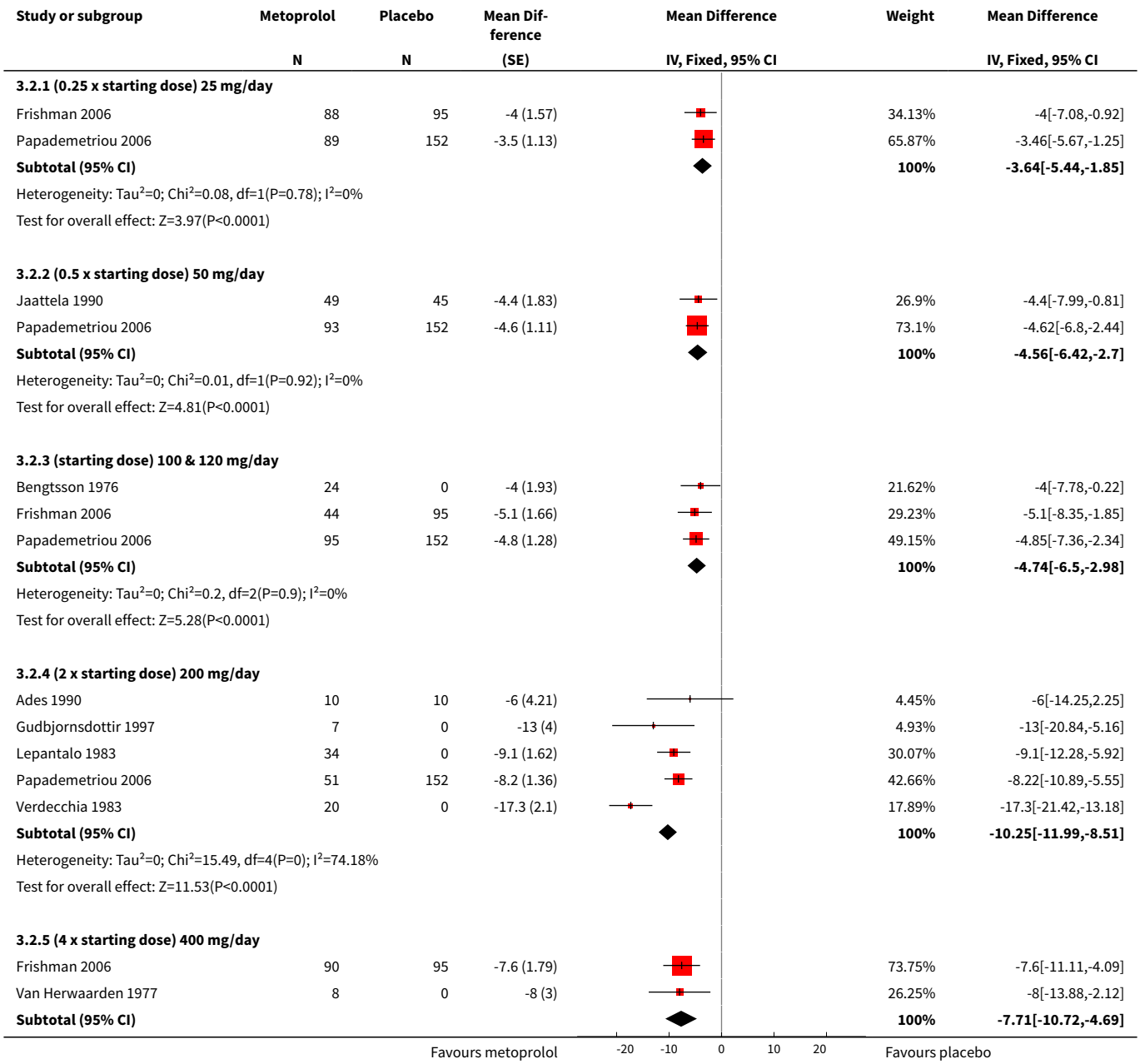


Favours metoprolol — Favours placebo



Study or subgroup	Metoprolol N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Frishman 2006	90	95	-8.2 (2.59)		78.84%	-8.2[-13.28,-3.12]
Van Herwaarden 1977	8	0	-21 (5)		21.16%	-21[-30.8,-11.2]
Subtotal (95% CI)					**100%**	**-10.91[-15.42,-6.4]**
Heterogeneity: Tau²=0; Chi²=5.17, df=1(P=0.02); I²=80.65%						
Test for overall effect: Z=4.74(P<0.0001)						
Test for subgroup differences: Chi²=13.39, df=1 (P=0.01), I²=70.12%						

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



Study or subgroup	Metoprolol N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
3.2.1 (0.25 x starting dose) 25 mg/day						
Frishman 2006	88	95	-4 (1.57)		34.13%	-4[-7.08,-0.92]
Papademetriou 2006	89	152	-3.5 (1.13)		65.87%	-3.46[-5.67,-1.25]
Subtotal (95% CI)					**100%**	**-3.64[-5.44,-1.85]**
Heterogeneity: Tau²=0; Chi²=0.08, df=1(P=0.78); I²=0%						
Test for overall effect: Z=3.97(P<0.0001)						
3.2.2 (0.5 x starting dose) 50 mg/day						
Jaattela 1990	49	45	-4.4 (1.83)		26.9%	-4.4[-7.99,-0.81]
Papademetriou 2006	93	152	-4.6 (1.11)		73.1%	-4.62[-6.8,-2.44]
Subtotal (95% CI)					**100%**	**-4.56[-6.42,-2.7]**
Heterogeneity: Tau²=0; Chi²=0.01, df=1(P=0.92); I²=0%						
Test for overall effect: Z=4.81(P<0.0001)						
3.2.3 (starting dose) 100 & 120 mg/day						
Bengtsson 1976	24	0	-4 (1.93)		21.62%	-4[-7.78,-0.22]
Frishman 2006	44	95	-5.1 (1.66)		29.23%	-5.1[-8.35,-1.85]
Papademetriou 2006	95	152	-4.8 (1.28)		49.15%	-4.85[-7.36,-2.34]
Subtotal (95% CI)					**100%**	**-4.74[-6.5,-2.98]**
Heterogeneity: Tau²=0; Chi²=0.2, df=2(P=0.9); I²=0%						
Test for overall effect: Z=5.28(P<0.0001)						
3.2.4 (2 x starting dose) 200 mg/day						
Ades 1990	10	10	-6 (4.21)		4.45%	-6[-14.25,2.25]
Gudbjornsdottir 1997	7	0	-13 (4)		4.93%	-13[-20.84,-5.16]
Lepantalo 1983	34	0	-9.1 (1.62)		30.07%	-9.1[-12.28,-5.92]
Papademetriou 2006	51	152	-8.2 (1.36)		42.66%	-8.22[-10.89,-5.55]
Verdecchia 1983	20	0	-17.3 (2.1)		17.89%	-17.3[-21.42,-13.18]
Subtotal (95% CI)					**100%**	**-10.25[-11.99,-8.51]**
Heterogeneity: Tau²=0; Chi²=15.49, df=4(P=0); I²=74.18%						
Test for overall effect: Z=11.53(P<0.0001)						
3.2.5 (4 x starting dose) 400 mg/day						
Frishman 2006	90	95	-7.6 (1.79)		73.75%	-7.6[-11.11,-4.09]
Van Herwaarden 1977	8	0	-8 (3)		26.25%	-8[-13.88,-2.12]
Subtotal (95% CI)					**100%**	**-7.71[-10.72,-4.69]**

Study or subgroup	Metoprolol N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=0.01, df=1(P=0.91); I²=0%						
Test for overall effect: Z=5.01(P<0.0001)						
Test for subgroup differences: Chi²=34.95, df=1 (P<0.0001), I²=88.55%						

Favours metoprolol -20 -10 0 10 20 Favours placebo

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

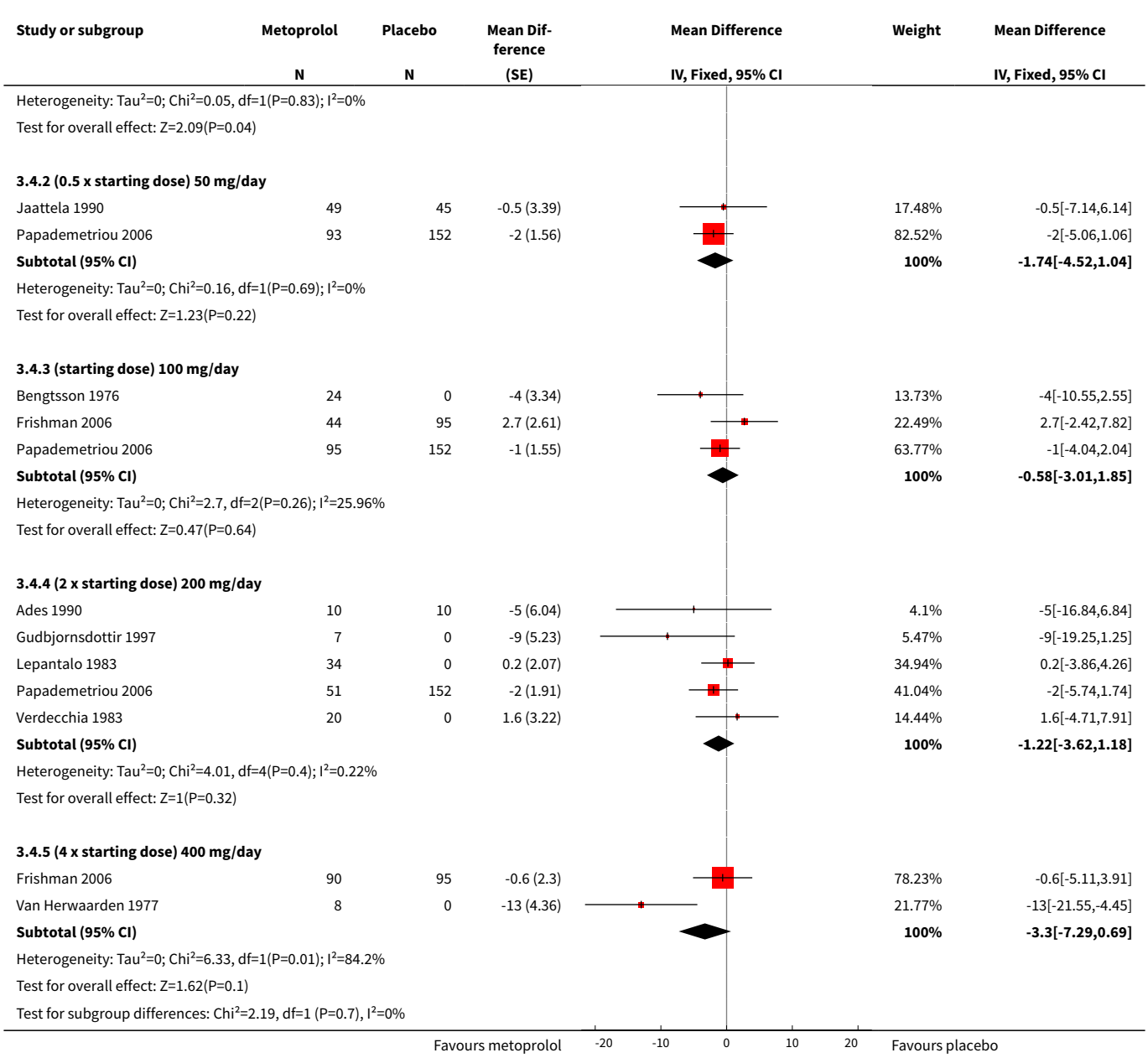
Study or subgroup	Metoprolol N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
3.3.1 (0.5 x starting dose) 50 mg/day						
Jaattela 1990	49	45	-5.6 (2.26)		100%	-5.6[-10.03,-1.17]
Subtotal (95% CI)					**100%**	**-5.6[-10.03,-1.17]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.48(P=0.01)						
3.3.2 (starting dose) 100 & 120 mg/day						
Bengtsson 1976	24	0	-15 (2)		100%	-15[-18.92,-11.08]
Subtotal (95% CI)					**100%**	**-15[-18.92,-11.08]**
Heterogeneity: Not applicable						
Test for overall effect: Z=7.5(P<0.0001)						
3.3.3 (2 x starting dose) 200 mg/day						
Ades 1990	10	10	-15 (4.74)		16.67%	-15[-24.29,-5.71]
Verdecchia 1983	20	0	-12.9 (2.12)		83.33%	-12.9[-17.06,-8.74]
Subtotal (95% CI)					**100%**	**-13.25[-17.04,-9.46]**
Heterogeneity: Tau²=0; Chi²=0.16, df=1(P=0.69); I²=0%						
Test for overall effect: Z=6.85(P<0.0001)						
3.3.4 (4 x starting dose) 400 mg/day						
Van Herwaarden 1977	8	0	-20 (3)		100%	-20[-25.88,-14.12]
Subtotal (95% CI)					**100%**	**-20[-25.88,-14.12]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%						
Test for overall effect: Z=6.67(P<0.0001)						
Test for subgroup differences: Chi²=17.17, df=1 (P=0), I²=82.53%						

Favours metoprolol -20 -10 0 10 20 Favours placebo

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

Study or subgroup	Metoprolol N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
3.4.1 (0.25 x starting dose) 25 mg/day						
Frishman 2006	88	95	-2.3 (2.23)		33.42%	-2.3[-6.67,2.07]
Papademetriou 2006	89	152	-2.9 (1.58)		66.58%	-2.9[-6,0.2]
Subtotal (95% CI)					**100%**	**-2.7[-5.23,-0.17]**

Favours metoprolol -20 -10 0 10 20 Favours placebo



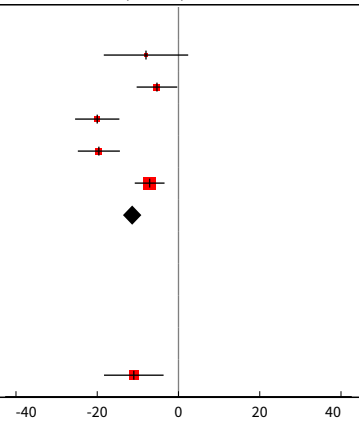
Comparison 4. Bisoprolol vs placebo

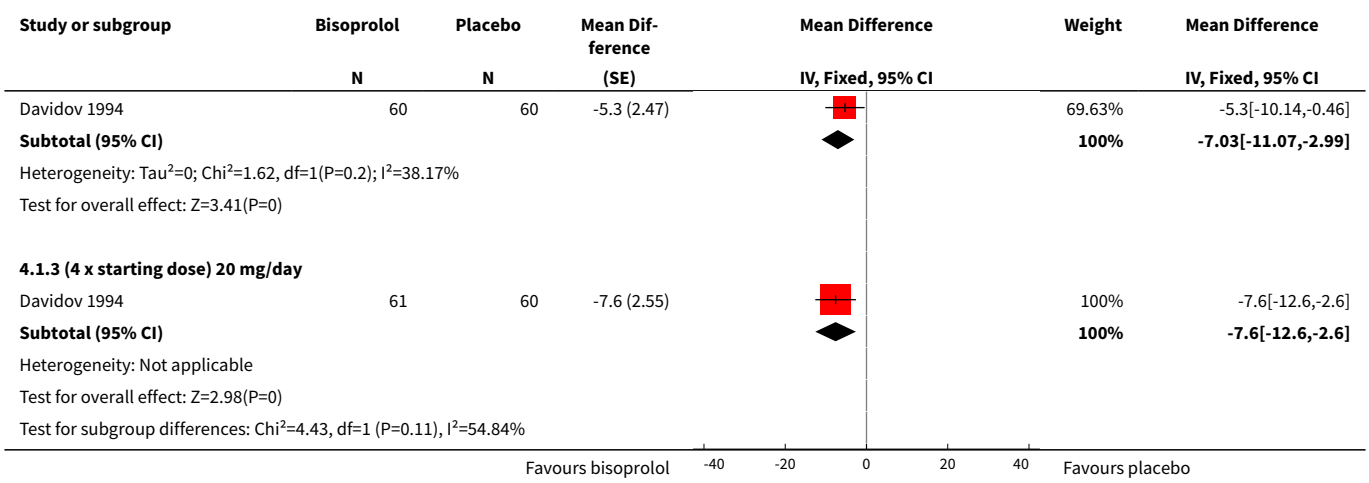
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SBP	6		Mean Difference (Fixed, 95% CI)	Subtotals only
1.1 (starting dose) 5 mg/day	5	422	Mean Difference (Fixed, 95% CI)	-11.40 [-13.67, -9.13]
1.2 (2 x starting dose) 10 mg/day	2	134	Mean Difference (Fixed, 95% CI)	-7.03 [-11.07, -2.99]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 (4 x starting dose) 20 mg/day	1	121	Mean Difference (Fixed, 95% CI)	-7.6 [-12.60, -2.60]
2 DBP	7		Mean Difference (Fixed, 95% CI)	Subtotals only
2.1 (starting dose) 5 mg/day	6	462	Mean Difference (Fixed, 95% CI)	-8.16 [-9.49, -6.84]
2.2 (2 x starting dose) 10 mg/day	3	173	Mean Difference (Fixed, 95% CI)	-7.44 [-9.88, -5.01]
2.3 (4 x starting dose) 20 mg/day	1	121	Mean Difference (Fixed, 95% CI)	-8.5 [-11.56, -5.44]
3 Heart rate	6		Mean Difference (Fixed, 95% CI)	Subtotals only
3.1 (starting dose) 5 mg/day	5	236	Mean Difference (Fixed, 95% CI)	-6.91 [-8.82, -4.99]
3.2 (2 x starting dose) 10 mg/day	3	173	Mean Difference (Fixed, 95% CI)	-10.19 [-12.87, -7.52]
3.3 (4 x starting dose) 20 mg/day	1	121	Mean Difference (Fixed, 95% CI)	-11.1 [-14.98, -7.22]
4 Pulse pressure	6		Mean Difference (Fixed, 95% CI)	Subtotals only
4.1 (starting dose) 5 mg/day	5	422	Mean Difference (Fixed, 95% CI)	-3.35 [-5.32, -1.38]
4.2 (2 x starting dose) 10 mg/day	2	134	Mean Difference (Fixed, 95% CI)	1.65 [-1.96, 5.26]
4.3 (4 x starting dose) 20 mg/day	1	121	Mean Difference (Fixed, 95% CI)	0.9 [-3.45, 5.25]

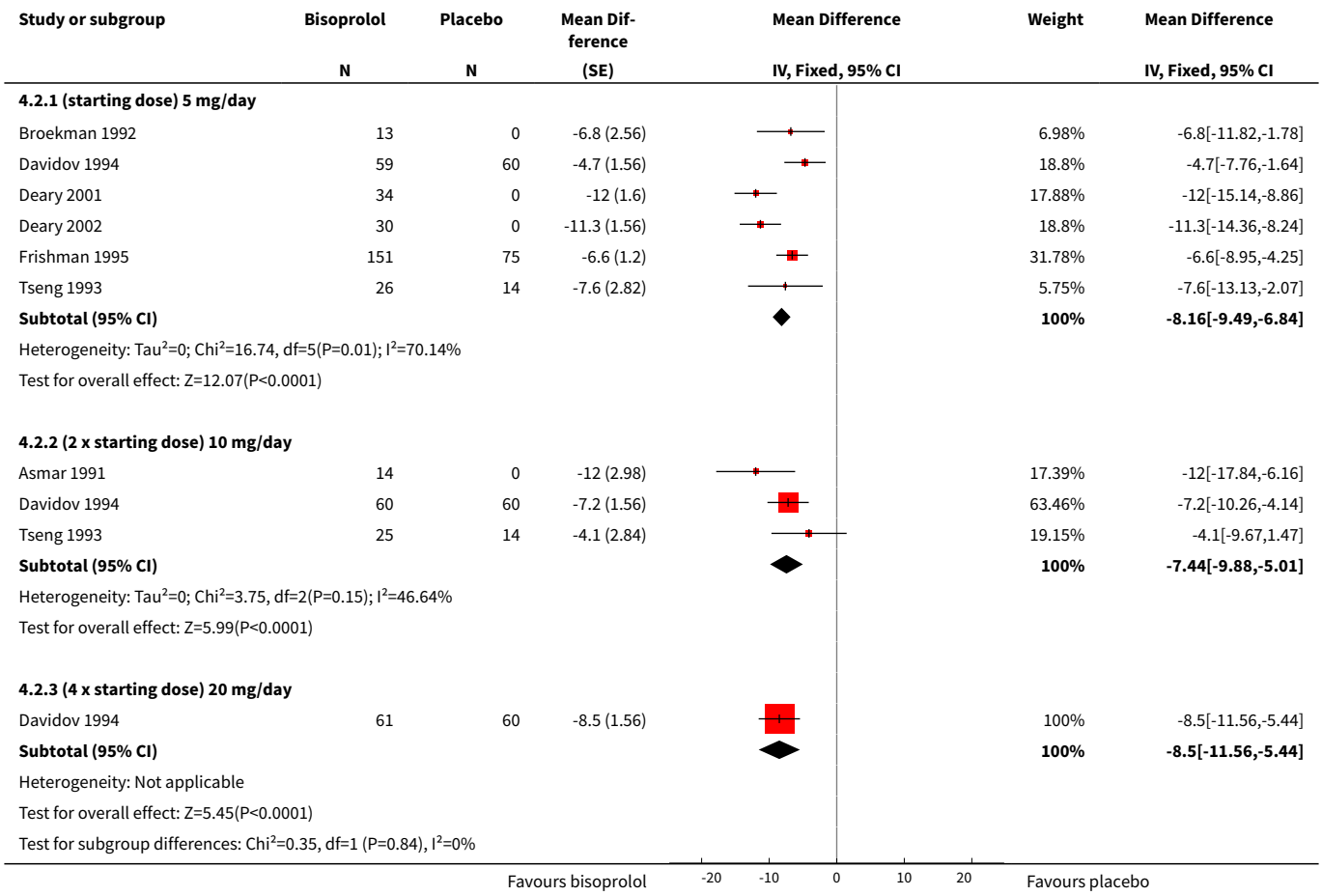
Analysis 4.1. Comparison 4 Bisoprolol vs placebo, Outcome 1 SBP.

Study or subgroup	Bisoprolol N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
4.1.1 (starting dose) 5 mg/day						
Broekman 1992	13	0	-8 (5.3)		4.76%	-8[-18.39,2.39]
Davidov 1994	59	60	-5.3 (2.55)		20.55%	-5.3[-10.3,-0.3]
Deary 2001	34	0	-20 (2.78)		17.29%	-20[-25.45,-14.55]
Deary 2002	30	0	-19.6 (2.64)		19.18%	-19.6[-24.77,-14.43]
Frishman 1995	151	75	-7.1 (1.87)		38.22%	-7.1[-10.77,-3.43]
Subtotal (95% CI)					**100%**	**-11.4[-13.67,-9.13]**
Heterogeneity: Tau²=0; Chi²=30.64, df=4(P<0.0001); I²=86.94%						
Test for overall effect: Z=9.86(P<0.0001)						
4.1.2 (2 x starting dose) 10 mg/day						
Asmar 1991	14	0	-11 (3.74)		30.37%	-11[-18.33,-3.67]



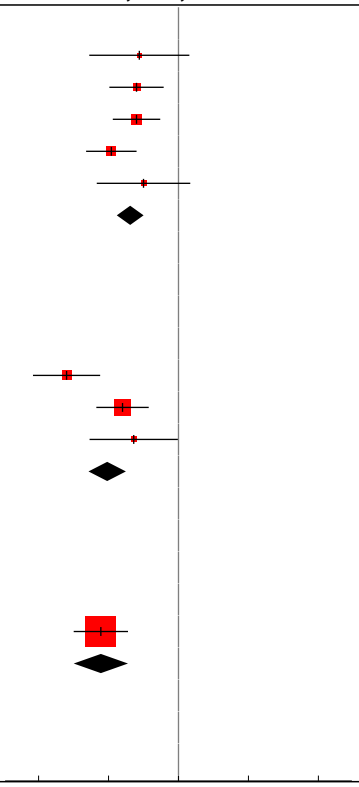


Analysis 4.2. Comparison 4 Bisoprolol vs placebo, Outcome 2 DBP.



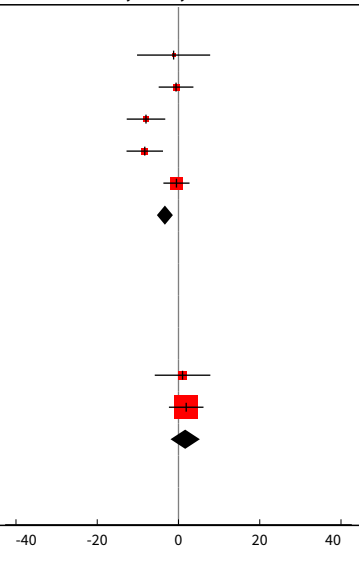
Analysis 4.3. Comparison 4 Bisoprolol vs placebo, Outcome 3 Heart rate.

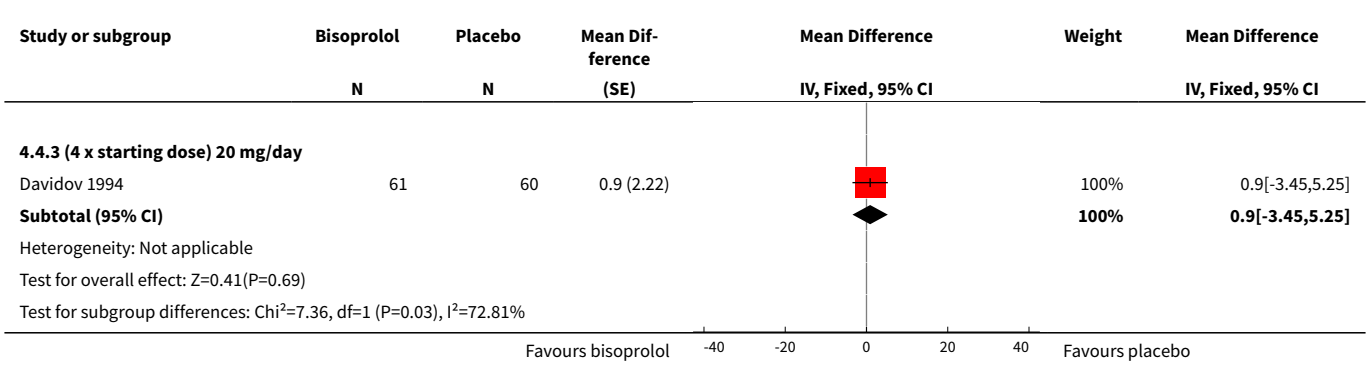
Study or subgroup	Bisoprolol N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
4.3.1 (starting dose) 5 mg/day						
Broekman 1992	13	0	-5.6 (3.65)		7.18%	-5.6[-12.75,1.55]
Davidov 1994	59	60	-6 (1.98)		24.39%	-6[-9.88,-2.12]
Deary 2001	34	0	-6 (1.73)		31.95%	-6[-9.39,-2.61]
Deary 2002	30	0	-9.6 (1.84)		28.25%	-9.6[-13.21,-5.99]
Tseng 1993	26	14	-5 (3.41)		8.22%	-5[-11.68,1.68]
Subtotal (95% CI)					**100%**	**-6.91[-8.82,-4.99]**
Heterogeneity: Tau²=0; Chi²=3.07, df=4(P=0.55); I²=0%						
Test for overall effect: Z=7.06(P<0.0001)						
4.3.2 (2 x starting dose) 10 mg/day						
Asmar 1991	14	0	-16 (2.45)		31.01%	-16[-20.8,-11.2]
Davidov 1994	60	60	-8 (1.91)		51.03%	-8[-11.74,-4.26]
Tseng 1993	25	14	-6.4 (3.22)		17.95%	-6.4[-12.71,-0.09]
Subtotal (95% CI)					**100%**	**-10.19[-12.87,-7.52]**
Heterogeneity: Tau²=0; Chi²=8.32, df=2(P=0.02); I²=75.97%						
Test for overall effect: Z=7.47(P<0.0001)						
4.3.3 (4 x starting dose) 20 mg/day						
Davidov 1994	61	60	-11.1 (1.98)		100%	-11.1[-14.98,-7.22]
Subtotal (95% CI)					**100%**	**-11.1[-14.98,-7.22]**
Heterogeneity: Not applicable						
Test for overall effect: Z=5.61(P<0.0001)						
Test for subgroup differences: Chi²=5.92, df=1 (P=0.05), I²=66.2%						



Analysis 4.4. Comparison 4 Bisoprolol vs placebo, Outcome 4 Pulse pressure.

Study or subgroup	Bisoprolol N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
4.4.1 (starting dose) 5 mg/day						
Broekman 1992	13	0	-1.2 (4.59)		4.79%	-1.2[-10.2,7.8]
Davidov 1994	59	60	-0.6 (2.18)		21.23%	-0.6[-4.87,3.67]
Deary 2001	34	0	-8 (2.42)		17.23%	-8[-12.74,-3.26]
Deary 2002	30	0	-8.3 (2.29)		19.24%	-8.3[-12.79,-3.81]
Frishman 1995	151	75	-0.5 (1.64)		37.51%	-0.5[-3.71,2.71]
Subtotal (95% CI)					**100%**	**-3.35[-5.32,-1.38]**
Heterogeneity: Tau²=0; Chi²=13.2, df=4(P=0.01); I²=69.69%						
Test for overall effect: Z=3.33(P=0)						
4.4.2 (2 x starting dose) 10 mg/day						
Asmar 1991	14	0	1 (3.49)		27.88%	1[-5.84,7.84]
Davidov 1994	60	60	1.9 (2.17)		72.12%	1.9[-2.35,6.15]
Subtotal (95% CI)					**100%**	**1.65[-1.96,5.26]**
Heterogeneity: Tau²=0; Chi²=0.05, df=1(P=0.83); I²=0%						
Test for overall effect: Z=0.89(P=0.37)						





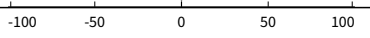
Comparison 5. Betaxolol vs Placebo

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 (0.5 x starting dose) 5 mg/day	1	148	Mean Difference (Fixed, 95% CI)	-5.81 [-10.55, -1.07]
1.2 (starting dose) 10 mg/day	1	146	Mean Difference (Fixed, 95% CI)	-8.2 [-12.94, -3.46]
1.3 (2 x starting dose) 20 mg/day	2	477	Mean Difference (Fixed, 95% CI)	-11.25 [-13.21, -9.29]
2 DBP	2		Mean Difference (Fixed, 95% CI)	Subtotals only
2.1 (0.5 x starting dose) 5 mg/day	1	148	Mean Difference (Fixed, 95% CI)	-3.8 [-6.54, -1.06]
2.2 (starting dose) 10 mg/day	1	146	Mean Difference (Fixed, 95% CI)	-6.5 [-9.24, -3.76]
2.3 (2 x starting dose) 20 mg/day	2	477	Mean Difference (Fixed, 95% CI)	-7.94 [-9.17, -6.71]
3 Heart rate	2		Mean Difference (Fixed, 95% CI)	Subtotals only
3.1 (0.5 x starting dose) 5 mg/day	1	148	Mean Difference (Fixed, 95% CI)	-7.4 [-10.34, -4.46]
3.2 (starting dose) 10 mg/day	1	146	Mean Difference (Fixed, 95% CI)	-8.2 [-11.14, -5.26]
3.3 (2 x starting dose) 20 mg/day	2	477	Mean Difference (Fixed, 95% CI)	-13.40 [-15.03, -11.77]
4 Pulse pressure	2		Mean Difference (Fixed, 95% CI)	Subtotals only
4.1 (0.5x starting dose) 5 mg/day	1	148	Mean Difference (Fixed, 95% CI)	-1.1 [-5.24, 3.04]
4.2 (starting dose) 10 mg/day	1	146	Mean Difference (Fixed, 95% CI)	-1.7 [-5.84, 2.44]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.3 (2 x starting dose) 20 mg/day	2	477	Mean Difference (Fixed, 95% CI)	-3.26 [-5.00, -1.52]

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

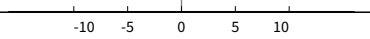
Study or subgroup	Betaxolol N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
5.1.1 (0.5 x starting dose) 5 mg/day						
Williams 1992	76	72	-5.8 (2.42)		100%	-5.81[-10.55,-1.07]
Subtotal (95% CI)					**100%**	**-5.81[-10.55,-1.07]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.4(P=0.02)						
5.1.2 (starting dose) 10 mg/day						
Williams 1992	74	72	-8.2 (2.42)		100%	-8.2[-12.94,-3.46]
Subtotal (95% CI)					**100%**	**-8.2[-12.94,-3.46]**
Heterogeneity: Not applicable						
Test for overall effect: Z=3.39(P=0)						
5.1.3 (2 x starting dose) 20 mg/day						
Williams 1992	74	72	-8.6 (2.42)		17.12%	-8.6[-13.34,-3.86]
Ameling 1991	331	0	-11.8 (1.1)		82.88%	-11.8[-13.96,-9.64]
Subtotal (95% CI)					**100%**	**-11.25[-13.21,-9.29]**
Heterogeneity: Tau^2=0; Chi^2=1.45, df=1(P=0.23); I^2=30.99%						
Test for overall effect: Z=11.24(P<0.0001)						
Test for subgroup differences: Chi^2=5.08, df=1 (P=0.08), I^2=60.6%						



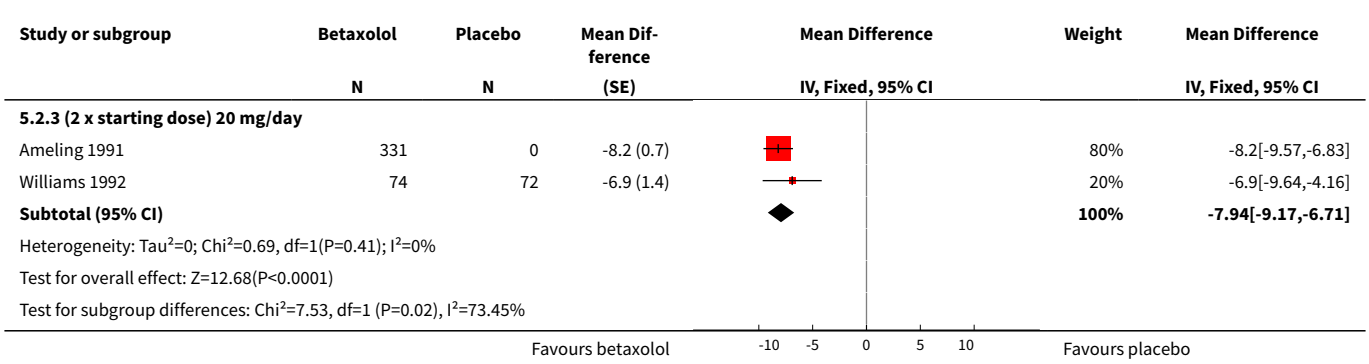
Favours betaxolol — Favours placebo

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

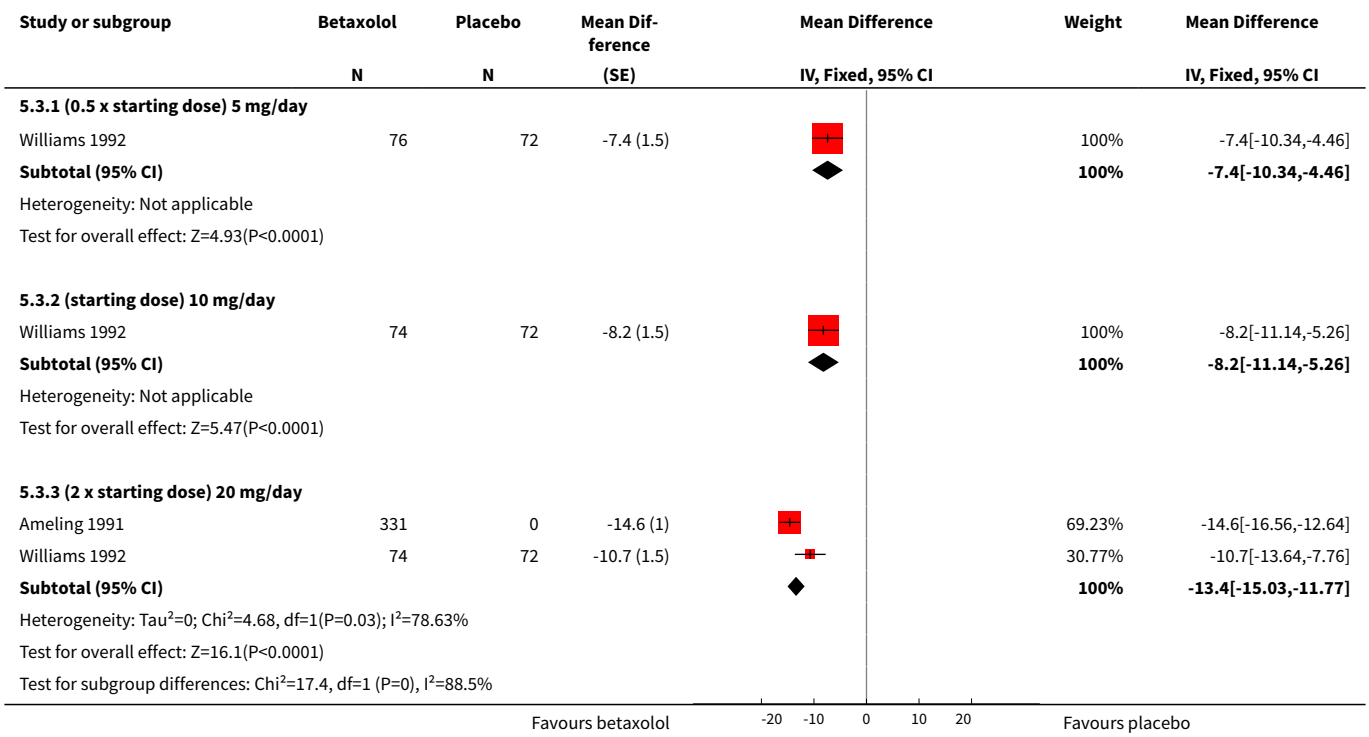
Study or subgroup	Betaxolol N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
5.2.1 (0.5 x starting dose) 5 mg/day						
Williams 1992	76	72	-3.8 (1.4)		100%	-3.8[-6.54,-1.06]
Subtotal (95% CI)					**100%**	**-3.8[-6.54,-1.06]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.71(P=0.01)						
5.2.2 (starting dose) 10 mg/day						
Williams 1992	74	72	-6.5 (1.4)		100%	-6.5[-9.24,-3.76]
Subtotal (95% CI)					**100%**	**-6.5[-9.24,-3.76]**
Heterogeneity: Not applicable						
Test for overall effect: Z=4.64(P<0.0001)						



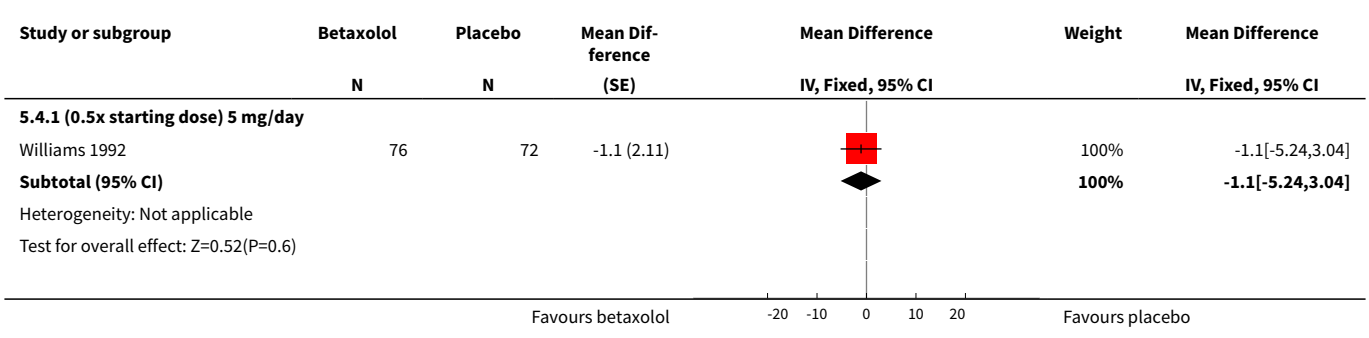
Favours betaxolol — Favours placebo

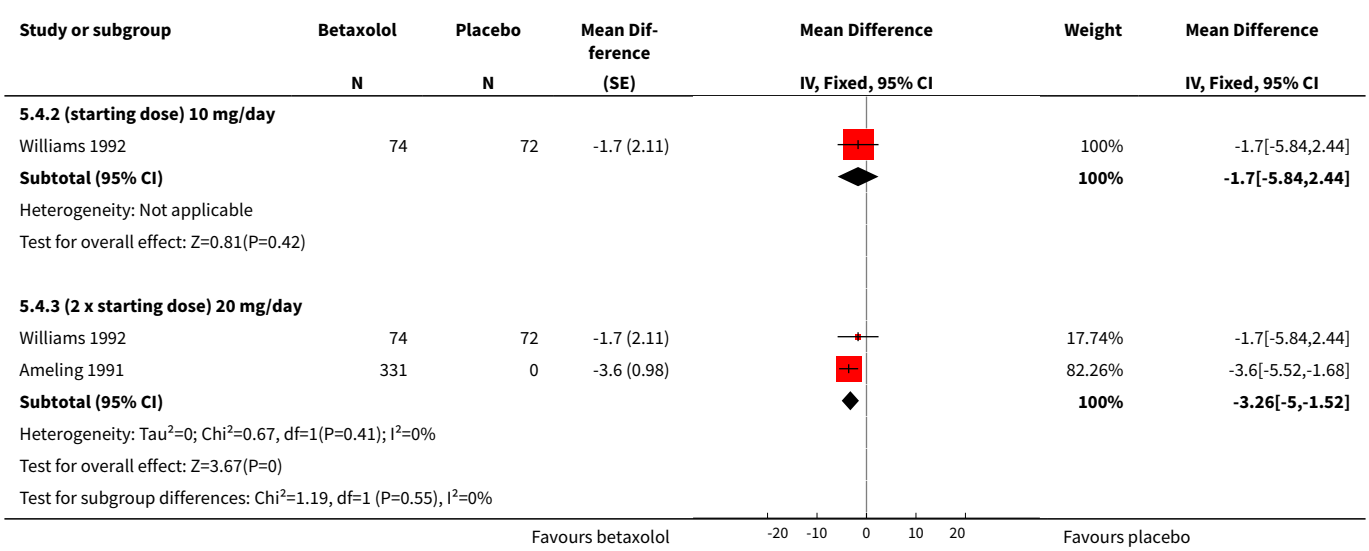


Analysis 5.3. Comparison 5 Betaxolol vs Placebo, Outcome 3 Heart rate.



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





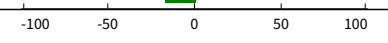
Comparison 6. Bevantolol vs Placebo

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 Bevantolol 100mg/day	1	35	Mean Difference (IV, Fixed, 95% CI)	-13.0 [-29.57, 3.57]
1.2 Bevantolol 200mg/day	1	35	Mean Difference (IV, Fixed, 95% CI)	-9.0 [-25.57, 7.57]
1.3 Bevantolol 300mg/day	1	35	Mean Difference (IV, Fixed, 95% CI)	-7.0 [-23.57, 9.57]
1.4 Bevantolol 400mg/day	1	35	Mean Difference (IV, Fixed, 95% CI)	-8.0 [-24.57, 8.57]
2 DBP	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Bevantolol 100mg/day	1	35	Mean Difference (IV, Fixed, 95% CI)	-5.0 [-15.52, 5.52]
2.2 Bevantolol 200mg/day	1	35	Mean Difference (IV, Fixed, 95% CI)	-9.0 [-19.52, 1.52]
2.3 Bevantolol 300mg/day	1	35	Mean Difference (IV, Fixed, 95% CI)	-9.0 [-19.52, 1.52]
2.4 Bevantolol 400mg/day	1	35	Mean Difference (IV, Fixed, 95% CI)	-10.0 [-20.52, 0.52]
3 Heart rate	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Bevantolol 100mg/day	1	35	Mean Difference (IV, Fixed, 95% CI)	-13.0 [-29.57, 3.57]
3.2 Bevantolol 200mg/day	1	35	Mean Difference (IV, Fixed, 95% CI)	-9.0 [-25.57, 7.57]
3.3 Bevantolol 300mg/day	1	35	Mean Difference (IV, Fixed, 95% CI)	-7.0 [-23.57, 9.57]
3.4 Bevantolol 400mg/day	1	35	Mean Difference (IV, Fixed, 95% CI)	-8.0 [-24.57, 8.57]
4 Pulse pressure	1		Mean Difference (Fixed, 95% CI)	Subtotals only
4.1 Bevantolol 100mg/day	1		Mean Difference (Fixed, 95% CI)	-8.0 [-22.52, 6.52]
4.2 Bevantolol 200mg/day	1		Mean Difference (Fixed, 95% CI)	0.0 [-14.52, 14.52]
4.3 Bevantolol 300mg/day	1		Mean Difference (Fixed, 95% CI)	2.0 [-12.56, 16.56]
4.4 Bevantolol 400mg/day	1		Mean Difference (Fixed, 95% CI)	2.0 [-12.52, 16.52]

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

Study or subgroup	Bevantolol N	Bevantolol Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
6.1.1 Bevantolol 100mg/day							
Okawa 1986	28	-19 (20.8)	7	-6 (19.8)		100%	-13[-29.57,3.57]
Subtotal ***	**28**		**7**			**100%**	**-13[-29.57,3.57]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.54(P=0.12)							
6.1.2 Bevantolol 200mg/day							
Okawa 1986	28	-15 (20.8)	7	-6 (19.8)		100%	-9[-25.57,7.57]
Subtotal ***	**28**		**7**			**100%**	**-9[-25.57,7.57]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.06(P=0.29)							
6.1.3 Bevantolol 300mg/day							
Okawa 1986	28	-13 (20.8)	7	-6 (19.8)		100%	-7[-23.57,9.57]
Subtotal ***	**28**		**7**			**100%**	**-7[-23.57,9.57]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.83(P=0.41)							
6.1.4 Bevantolol 400mg/day							
Okawa 1986	28	-14 (20.8)	7	-6 (19.8)		100%	-8[-24.57,8.57]



Favours bevantolol — Favours placebo

Study or subgroup	Bevantolol N	Bevantolol Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Subtotal ***	**28**		**7**			**100%**	**-8[-24.57,8.57]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.95(P=0.34)							
Test for subgroup differences: Chi^2=0.29, df=1 (P=0.96), I^2=0%							

Favours bevantolol -100 -50 0 50 100 Favours placebo

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

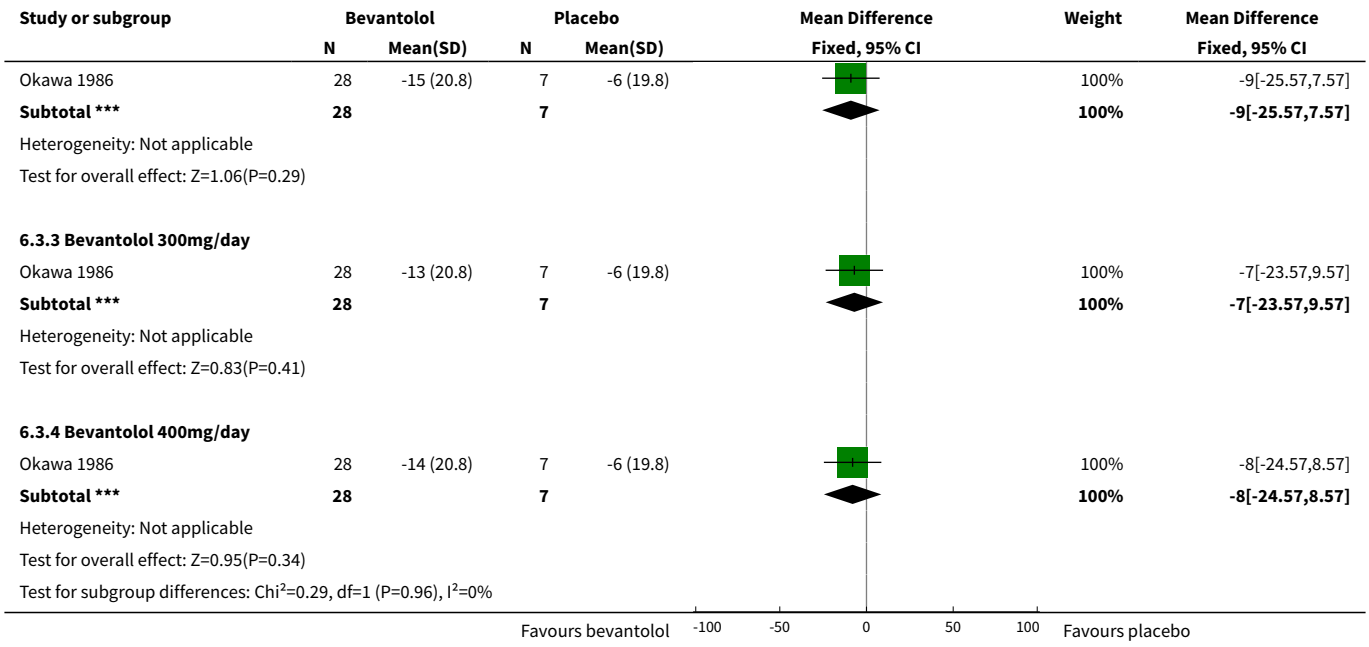
Study or subgroup	Bevantolol N	Bevantolol Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
6.2.1 Bevantolol 100mg/day							
Okawa 1986	28	-12 (13.1)	7	-7 (12.6)		100%	-5[-15.52,5.52]
Subtotal ***	**28**		**7**			**100%**	**-5[-15.52,5.52]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.93(P=0.35)							
6.2.2 Bevantolol 200mg/day							
Okawa 1986	28	-16 (13.1)	7	-7 (12.6)		100%	-9[-19.52,1.52]
Subtotal ***	**28**		**7**			**100%**	**-9[-19.52,1.52]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.68(P=0.09)							
6.2.3 Bevantolol 300mg/day							
Okawa 1986	28	-16 (13.1)	7	-7 (12.6)		100%	-9[-19.52,1.52]
Subtotal ***	**28**		**7**			**100%**	**-9[-19.52,1.52]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.68(P=0.09)							
6.2.4 Bevantolol 400mg/day							
Okawa 1986	28	-17 (13.1)	7	-7 (12.6)		100%	-10[-20.52,0.52]
Subtotal ***	**28**		**7**			**100%**	**-10[-20.52,0.52]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.86(P=0.06)							
Test for subgroup differences: Chi^2=0.51, df=1 (P=0.92), I^2=0%							

Favours bevantolol -100 -50 0 50 100 Favours placebo

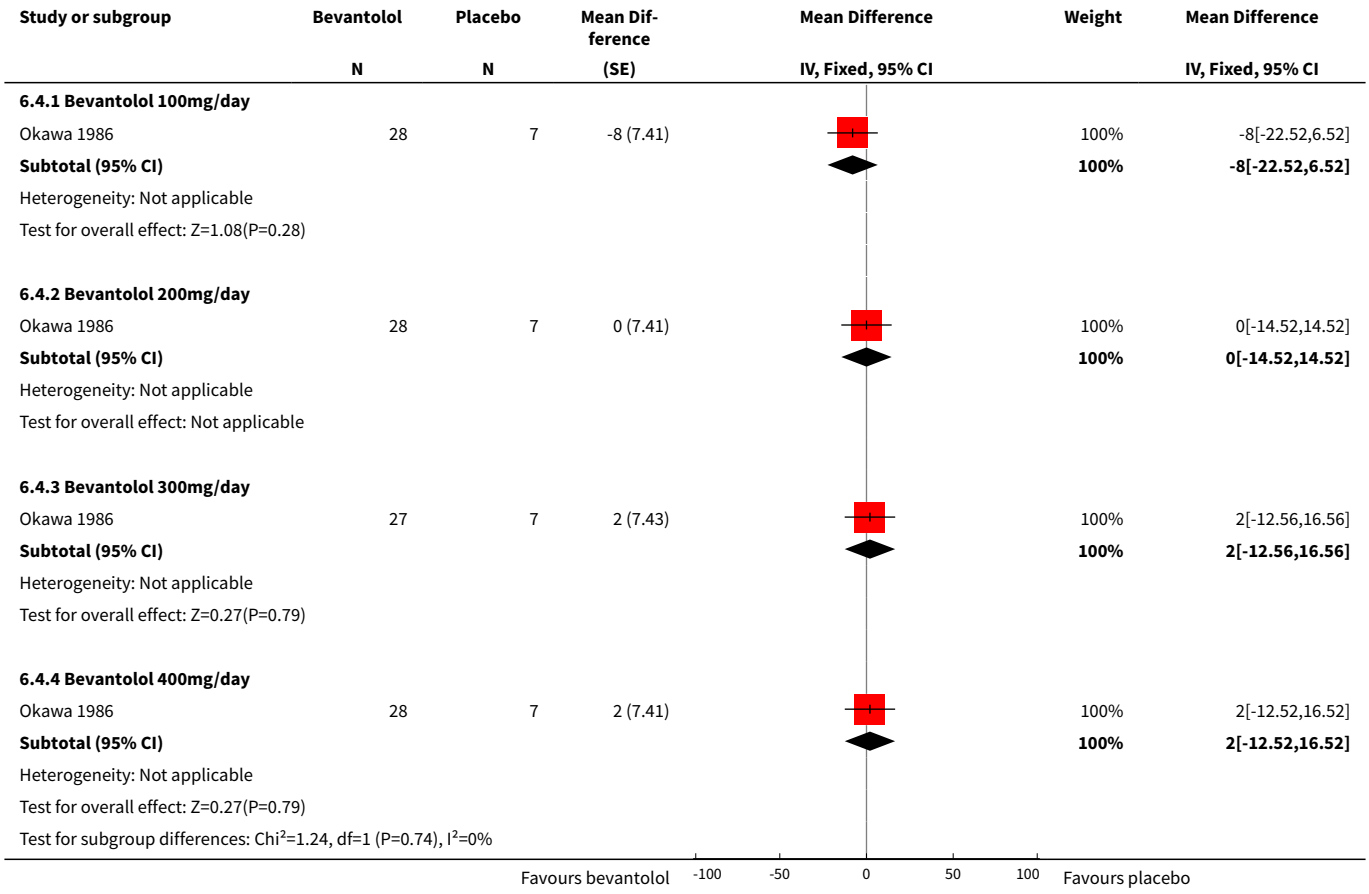
Analysis 6.3. Comparison 6 Bevantolol vs Placebo, Outcome 3 Heart rate.

Study or subgroup	Bevantolol N	Bevantolol Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
6.3.1 Bevantolol 100mg/day							
Okawa 1986	28	-19 (20.8)	7	-6 (19.8)		100%	-13[-29.57,3.57]
Subtotal ***	**28**		**7**			**100%**	**-13[-29.57,3.57]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.54(P=0.12)							
6.3.2 Bevantolol 200mg/day							

Favours bevantolol -100 -50 0 50 100 Favours placebo



Analysis 6.4. Comparison 6 Bevantolol vs Placebo, Outcome 4 Pulse pressure.

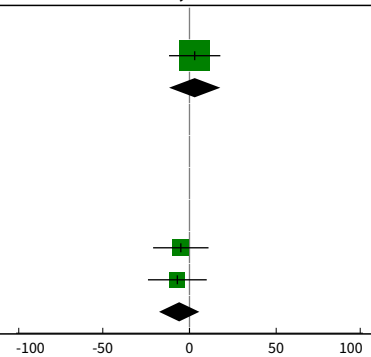


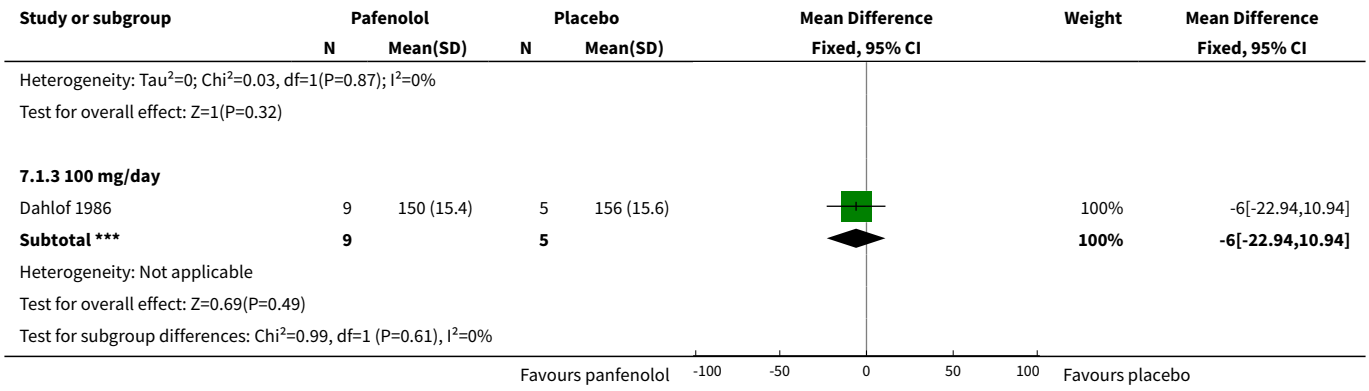
Comparison 7. Pafenolol vs Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SBP	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 25 mg/day	1	21	Mean Difference (IV, Fixed, 95% CI)	3.0 [-11.79, 17.79]
1.2 50 mg/day	2	33	Mean Difference (IV, Fixed, 95% CI)	-5.94 [-17.57, 5.68]
1.3 100 mg/day	1	14	Mean Difference (IV, Fixed, 95% CI)	-6.0 [-22.94, 10.94]
2 DBP	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 25 mg/day	1	21	Mean Difference (IV, Fixed, 95% CI)	-8.0 [-16.73, 0.73]
2.2 50 mg/day	2	33	Mean Difference (IV, Fixed, 95% CI)	-4.41 [-11.22, 2.40]
2.3 100 mg/day	1	14	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-12.75, 8.75]
3 Heart rate	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 25 mg/day	1	21	Mean Difference (IV, Fixed, 95% CI)	-3.0 [-12.93, 6.93]
3.2 50 mg/day	2	33	Mean Difference (IV, Fixed, 95% CI)	-8.14 [-15.91, -0.36]
3.3 100 mg/day	1	14	Mean Difference (IV, Fixed, 95% CI)	-20.0 [-32.60, -7.40]
4 Pulse pressure	2		Mean Difference (Fixed, 95% CI)	Subtotals only
4.1 25 mg/day	1	21	Mean Difference (Fixed, 95% CI)	11.0 [-1.82, 23.82]
4.2 50 mg/day	2	33	Mean Difference (Fixed, 95% CI)	-1.75 [-11.86, 8.37]
4.3 100 mg/day	1	14	Mean Difference (Fixed, 95% CI)	-4.0 [-18.86, 10.86]

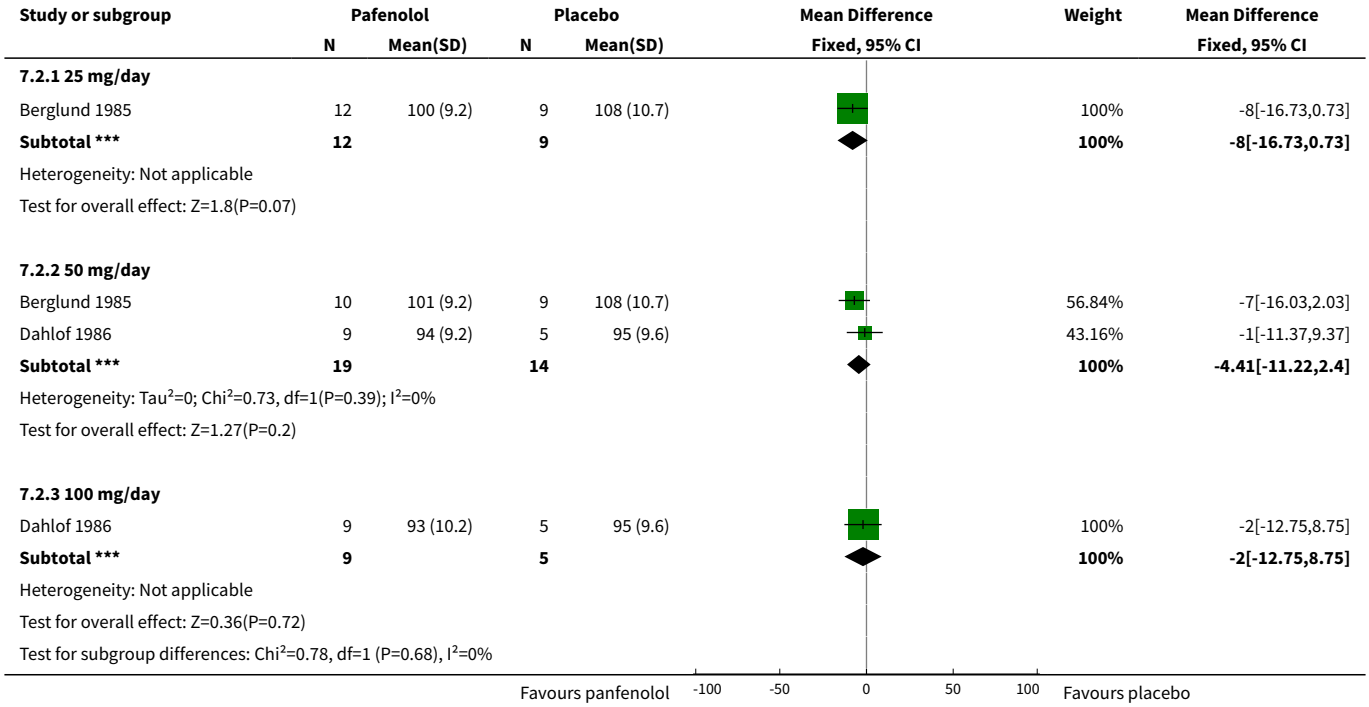
Analysis 7.1. Comparison 7 Pafenolol vs Placebo, Outcome 1 SBP.

Study or subgroup	Pafenolol N	Pafenolol Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
7.1.1 25 mg/day							
Berglund 1985	12	154 (15.4)	9	151 (18.3)		100%	3[-11.79,17.79]
Subtotal ***	**12**		**9**			**100%**	**3[-11.79,17.79]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.4(P=0.69)							
7.1.2 50 mg/day							
Berglund 1985	10	146 (17.1)	9	151 (18.3)		52.94%	-5[-20.98,10.98]
Dahlof 1986	9	149 (15.4)	5	156 (15.6)		47.06%	-7[-23.94,9.94]
Subtotal ***	**19**		**14**			**100%**	**-5.94[-17.57,5.68]**

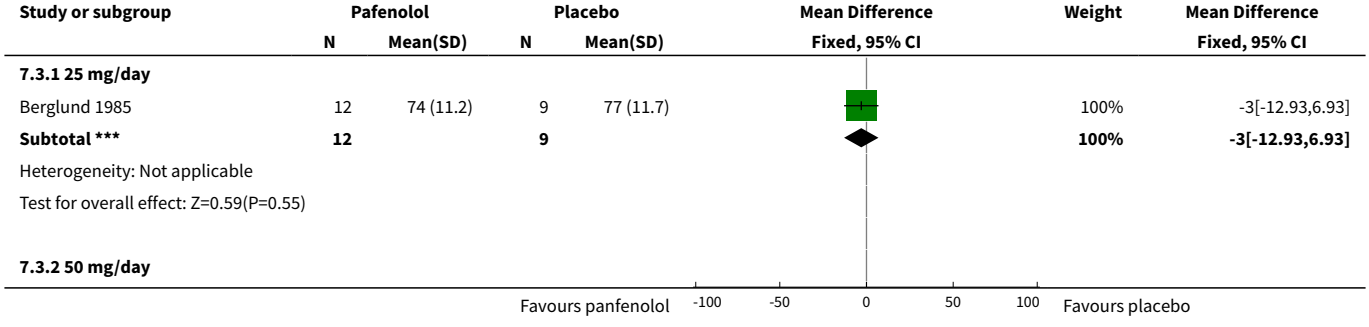


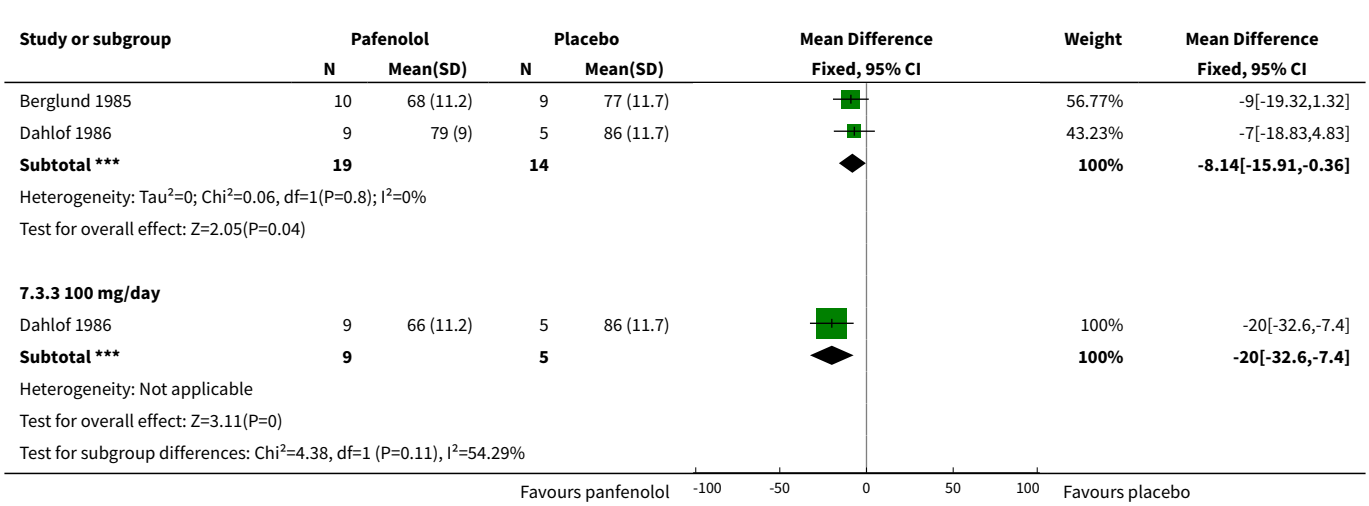


Analysis 7.2. Comparison 7 Pafenolol vs Placebo, Outcome 2 DBP.

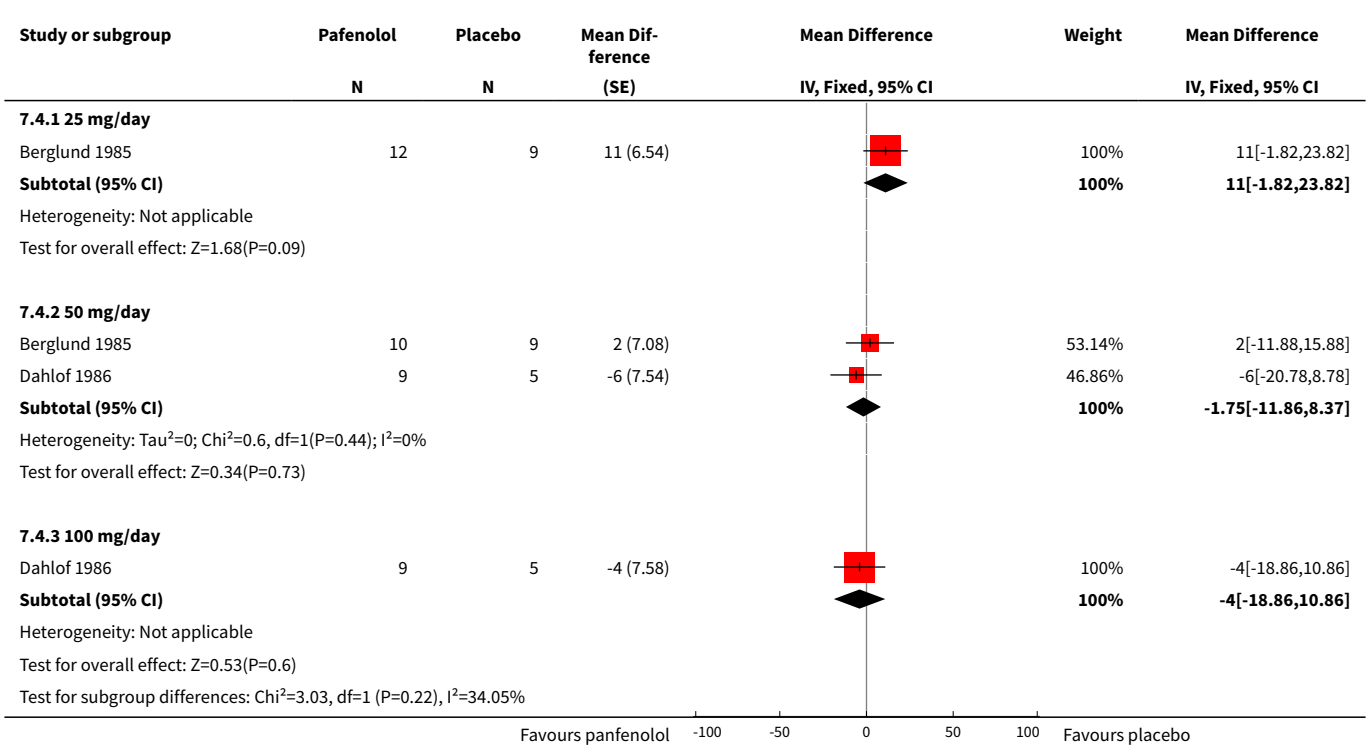


Analysis 7.3. Comparison 7 Pafenolol vs Placebo, Outcome 3 Heart rate.





Analysis 7.4. Comparison 7 Pafenolol vs Placebo, Outcome 4 Pulse pressure.



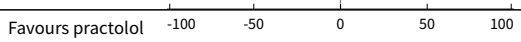
Comparison 8. Practolol vs Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SBP	1	24	Mean Difference (Fixed, 95% CI)	-21.2 [-29.31, -13.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Practolol 600mg/day	1	24	Mean Difference (Fixed, 95% CI)	-21.2 [-29.31, -13.09]
2 DBP	1	24	Mean Difference (Fixed, 95% CI)	-13.9 [-17.00, -8.80]
2.1 Practolol 600mg/day	1	24	Mean Difference (Fixed, 95% CI)	-13.9 [-17.00, -8.80]
3 Heart rate	1	24	Mean Difference (Fixed, 95% CI)	-14.0 [-21.45, -6.55]
3.1 Practolol 600mg/day	1	24	Mean Difference (Fixed, 95% CI)	-14.0 [-21.45, -6.55]
4 Pulse pressure	1	24	Mean Difference (Fixed, 95% CI)	-7.30 [-14.41, -0.19]
4.1 Practolol 600mg/day	1	24	Mean Difference (Fixed, 95% CI)	-7.30 [-14.41, -0.19]

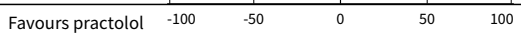
Analysis 8.1. Comparison 8 Practolol vs Placebo, Outcome 1 SBP.

Study or subgroup	Practolol N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
8.1.1 Practolol 600mg/day						
Petrie 1976	24	0	-21.2 (4.14)		100%	-21.2[-29.31,-13.09]
Subtotal (95% CI)					**100%**	**-21.2[-29.31,-13.09]**
Heterogeneity: Not applicable						
Test for overall effect: Z=5.12(P<0.0001)						
Total (95% CI)					**100%**	**-21.2[-29.31,-13.09]**
Heterogeneity: Not applicable						
Test for overall effect: Z=5.12(P<0.0001)						

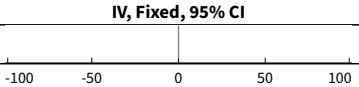


Analysis 8.2. Comparison 8 Practolol vs Placebo, Outcome 2 DBP.

Study or subgroup	Practolol N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
8.2.1 Practolol 600mg/day						
Petrie 1976	24	0	-13.9 (2.6)		100%	-13.9[-19,-8.8]
Subtotal (95% CI)					**100%**	**-13.9[-19,-8.8]**
Heterogeneity: Not applicable						
Test for overall effect: Z=5.35(P<0.0001)						
Total (95% CI)					**100%**	**-13.9[-19,-8.8]**
Heterogeneity: Not applicable						

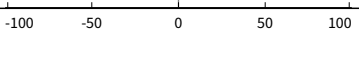


Study or subgroup	Practolol N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Test for overall effect: Z=5.35(P<0.0001)						



Analysis 8.3. Comparison 8 Practolol vs Placebo, Outcome 3 Heart rate.

Study or subgroup	Practolol N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
8.3.1 Practolol 600mg/day						
Petrie 1976	24	0	-14 (3.8)		100%	-14[-21.45,-6.55]
Subtotal (95% CI)					**100%**	**-14[-21.45,-6.55]**
Heterogeneity: Not applicable						
Test for overall effect: Z=3.68(P=0)						
Total (95% CI)					**100%**	**-14[-21.45,-6.55]**
Heterogeneity: Not applicable						
Test for overall effect: Z=3.68(P=0)						



Analysis 8.4. Comparison 8 Practolol vs Placebo, Outcome 4 Pulse pressure.

Study or subgroup	Practolol N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
8.4.1 Practolol 600mg/day						
Petrie 1976	24	0	-7.3 (3.63)		100%	-7.3[-14.41,-0.19]
Subtotal (95% CI)					**100%**	**-7.3[-14.41,-0.19]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%						
Test for overall effect: Z=2.01(P=0.04)						
Total (95% CI)					**100%**	**-7.3[-14.41,-0.19]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%						
Test for overall effect: Z=2.01(P=0.04)						

Comparison 9. Pooled overall effect

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SBP	50		Mean Difference (Fixed, 95% CI)	Subtotals only
1.1 0.25 x starting dose	5	790	Mean Difference (Fixed, 95% CI)	-5.34 [-7.29, -3.38]
1.2 0.5 x starting dose	7	941	Mean Difference (Fixed, 95% CI)	-5.71 [-7.59, -3.82]

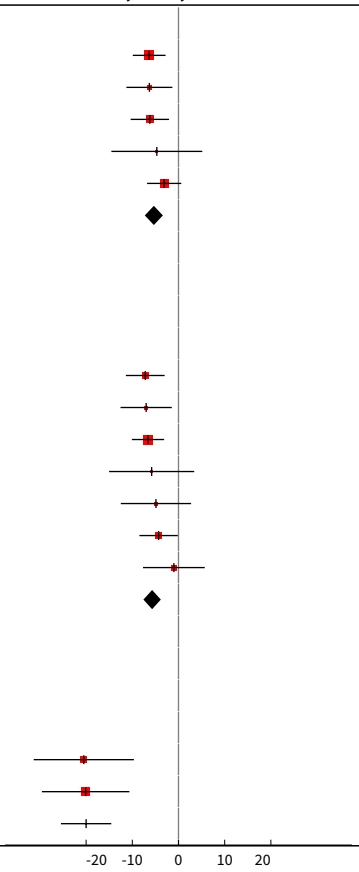
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 starting dose	30	2879	Mean Difference (Fixed, 95% CI)	-9.29 [-10.21, -8.38]
1.4 2 x starting dose	27	3026	Mean Difference (Fixed, 95% CI)	-10.58 [-11.45, -9.71]
1.5 4 x starting dose	9	1087	Mean Difference (Fixed, 95% CI)	-8.90 [-10.47, -7.34]
1.6 8 x starting dose	2	331	Mean Difference (Fixed, 95% CI)	-8.29 [-11.24, -5.35]
2 DBP	51		Mean Difference (Fixed, 95% CI)	Subtotals only
2.1 0.25 x starting dose	5	790	Mean Difference (Fixed, 95% CI)	-3.59 [-4.79, -2.39]
2.2 0.5 x starting dose	7	941	Mean Difference (Fixed, 95% CI)	-4.27 [-5.31, -3.22]
2.3 starting dose	31	2907	Mean Difference (Fixed, 95% CI)	-7.06 [-7.62, -6.51]
2.4 2 x starting dose	28	3065	Mean Difference (Fixed, 95% CI)	-8.92 [-9.47, -8.38]
2.5 4 x starting dose	9	1087	Mean Difference (Fixed, 95% CI)	-7.17 [-8.15, -6.18]
2.6 8 x starting dose	2	331	Mean Difference (Fixed, 95% CI)	-7.20 [-8.99, -5.40]
3 Heart rate	37		Mean Difference (Fixed, 95% CI)	Subtotals only
3.1 0.25 x starting dose	1	136	Mean Difference (Fixed, 95% CI)	-2.9 [-5.86, 0.06]
3.2 0.5 x starting dose	5	499	Mean Difference (Fixed, 95% CI)	-4.34 [-6.21, -2.47]
3.3 starting dose	20	1315	Mean Difference (Fixed, 95% CI)	-9.80 [-10.65, -8.94]
3.4 2 x starting dose	20	2175	Mean Difference (Fixed, 95% CI)	-11.33 [-12.06, -10.61]
3.5 4 x starting dose	8	556	Mean Difference (Fixed, 95% CI)	-13.71 [-15.00, -12.43]
3.6 8 x starting dose	2	331	Mean Difference (Fixed, 95% CI)	-9.19 [-11.21, -7.18]
4 Pulse pressure	50		Mean Difference (Fixed, 95% CI)	Subtotals only
4.1 0.25 x starting dose	5	790	Mean Difference (Fixed, 95% CI)	-1.72 [-3.43, -0.00]
4.2 0.5 x starting dose	7	941	Mean Difference (Fixed, 95% CI)	-1.48 [-3.13, 0.17]
4.3 starting dose	30	2913	Mean Difference (Fixed, 95% CI)	0.00 [-2.78, -1.22]
4.4 2 x starting dose	27	3026	Mean Difference (Fixed, 95% CI)	-1.39 [-2.14, -0.65]
4.5 4 x starting dose	9	1087	Mean Difference (Fixed, 95% CI)	-1.80 [-3.16, -0.44]
4.6 8 x starting dose	2	331	Mean Difference (Fixed, 95% CI)	-1.04 [-3.67, 1.60]
5 WDAE	3	2618	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.50, 1.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 SBP combined starting dose and 2 x starting dose	47	5246	Mean Difference (Fixed, 95% CI)	-10.42 [-11.11, -9.72]
6.1 starting dose	30	2509	Mean Difference (Fixed, 95% CI)	-9.71 [-10.75, -8.67]
6.2 2 x starting dose	27	2737	Mean Difference (Fixed, 95% CI)	-10.99 [-11.93, -10.06]
7 DBP combined starting dose and 2 x starting dose	48	5316	Mean Difference (Fixed, 95% CI)	-8.27 [-8.69, -7.84]
7.1 starting dose	31	2540	Mean Difference (Fixed, 95% CI)	-7.23 [-7.85, -6.60]
7.2 2x starting dose	28	2776	Mean Difference (Fixed, 95% CI)	-9.16 [-9.74, -8.58]
8 Heart rate combined starting dose and 2 x starting dose	33	3407	Mean Difference (Fixed, 95% CI)	-10.93 [-11.48, -10.37]
8.1 starting dose	20	1268	Mean Difference (Fixed, 95% CI)	-10.03 [-10.90, -9.17]
8.2 2 x starting dose	20	2139	Mean Difference (Fixed, 95% CI)	-11.57 [-12.30, -10.84]
9 Pulse pressure combined starting dose and 2 x starting dose	47	5246	Mean Difference (Fixed, 95% CI)	-1.76 [-2.34, -1.19]
9.1 starting dose	30	2509	Mean Difference (Fixed, 95% CI)	-2.09 [-2.94, -1.23]
9.2 2 x starting dose	27	2737	Mean Difference (Fixed, 95% CI)	-1.49 [-2.27, -0.71]
10 SBP test for 2 x starting dose subgroup difference	26	2197	Mean Difference (Fixed, 95% CI)	-11.27 [-12.22, -10.32]
10.1 Atenolol	12	495	Mean Difference (Fixed, 95% CI)	-15.34 [-16.86, -13.82]
10.2 Nebivolol	5	855	Mean Difference (Fixed, 95% CI)	-5.26 [-7.19, -3.34]
10.3 Metoprolol	5	284	Mean Difference (Fixed, 95% CI)	-11.54 [-14.37, -8.71]
10.4 Bisoprolol	2	134	Mean Difference (Fixed, 95% CI)	-7.03 [-11.07, -2.99]
10.5 Betaxolol	2	429	Mean Difference (Fixed, 95% CI)	-11.63 [-13.73, -9.53]
11 DBP test for 2 x starting dose subgroup difference	27	2236	Mean Difference (Fixed, 95% CI)	-9.47 [-10.06, -8.88]
11.1 Atenolol	12	495	Mean Difference (Fixed, 95% CI)	-12.91 [-13.89, -11.93]
11.2 Nebivolol	5	855	Mean Difference (Fixed, 95% CI)	-5.82 [-6.99, -4.65]
11.3 Metoprolol	5	284	Mean Difference (Fixed, 95% CI)	-10.25 [-11.99, -8.51]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.4 Bisoprolol	3	173	Mean Difference (Fixed, 95% CI)	-7.44 [-9.88, -5.01]
11.5 Betaxolol	2	429	Mean Difference (Fixed, 95% CI)	-8.08 [-9.39, -6.77]
12 Heart rate test for 2 x starting dose subgroup difference	19	1346	Mean Difference (Fixed, 95% CI)	-12.24 [-13.05, -11.42]
12.1 Atenolol	10	413	Mean Difference (Fixed, 95% CI)	-13.70 [-14.83, -12.56]
12.2 Nebivolol	2	291	Mean Difference (Fixed, 95% CI)	-5.94 [-7.98, -3.90]
12.3 Metoprolol	2	40	Mean Difference (Fixed, 95% CI)	-13.25 [-17.04, -9.46]
12.4 Bisoprolol	3	173	Mean Difference (Fixed, 95% CI)	-10.19 [-12.87, -7.52]
12.5 Betaxolol	2	429	Mean Difference (Fixed, 95% CI)	-14.43 [-16.35, -12.51]

Analysis 9.1. Comparison 9 Pooled overall effect, Outcome 1 SBP.

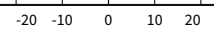
Study or subgroup	Beta blockers N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
9.1.1 0.25 x starting dose						
Papademetriou 2006	89	152	-6.3 (1.81)		30.45%	-6.35[-9.9,-2.8]
Frishman 2006	88	95	-6.3 (2.54)		15.46%	-6.3[-11.28,-1.32]
Van Nueten 1997	87	84	-6.2 (2.12)		22.2%	-6.2[-10.36,-2.04]
Lacourciere 1994	17	14	-4.7 (5.02)		3.96%	-4.69[-14.53,5.15]
Weiss 2007	83	81	-3.1 (1.89)		27.93%	-3.1[-6.8,0.6]
Subtotal (95% CI)					**100%**	**-5.34[-7.29,-3.38]**
Heterogeneity: Tau²=0; Chi²=2.04, df=4(P=0.73); I²=0%						
Test for overall effect: Z=5.34(P<0.0001)						
9.1.2 0.5 x starting dose						
Van Nueten 1997	85	84	-7.2 (2.14)		20.24%	-7.2[-11.39,-3.01]
Chrysant 1992	44	43	-7 (2.83)		11.57%	-7[-12.55,-1.45]
Papademetriou 2006	93	152	-6.6 (1.78)		29.25%	-6.6[-10.09,-3.11]
Williams 1992	76	24	-5.8 (4.7)		4.2%	-5.81[-15.02,3.4]
Jaattela 1990	49	45	-4.9 (3.88)		6.16%	-4.88[-12.48,2.72]
Weiss 2007	82	81	-4.3 (2.12)		20.62%	-4.3[-8.46,-0.14]
Saunders 2007	42	41	-1 (3.41)		7.97%	-1[-7.68,5.68]
Subtotal (95% CI)					**100%**	**-5.71[-7.59,-3.82]**
Heterogeneity: Tau²=0; Chi²=3.34, df=6(P=0.77); I²=0%						
Test for overall effect: Z=5.93(P<0.0001)						
9.1.3 starting dose						
Chan 1991	16	13	-20.5 (5.53)		0.71%	-20.5[-31.34,-9.66]
Chan 1992	18	14	-20.1 (4.83)		0.93%	-20.1[-29.57,-10.63]
Deary 2001	34	0	-20 (2.78)		2.81%	-20[-25.45,-14.55]



Study or subgroup	Beta blockers N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Deary 2002	30	0	-19.6 (2.64)		3.11%	-19.6[-24.77,-14.43]
Stornello 1991	12	0	-18.4 (4.18)		1.24%	-18.4[-26.59,-10.21]
Maclean 1990	37	32	-16 (3.54)		1.73%	-16[-22.94,-9.06]
Van Bortel 1993	80	0	-16 (2.38)		3.83%	-16[-20.66,-11.34]
Jeffers 1977	21	0	-14.3 (2.95)		2.49%	-14.3[-20.08,-8.52]
Baez 1986	12	12	-14 (4.81)		0.94%	-14[-23.43,-4.57]
Dhakam 2008	16	0	-13 (3)		2.41%	-13[-18.88,-7.12]
Dhakam 2008	16	0	-12 (3)		2.41%	-12[-17.88,-6.12]
Himmelmann 1996	15	0	-12 (3.14)		2.2%	-12[-18.15,-5.85]
Lacourciere 1994	19	14	-11.2 (4.9)		0.9%	-11.25[-20.85,-1.65]
Van Nueten 1998	110	119	-11 (1.84)		6.41%	-11[-14.61,-7.39]
Stumpe 1985	47	44	-11 (3.07)		2.3%	-11[-17.02,-4.98]
Van Nueten 1998	119	119	-10 (1.8)		6.7%	-10[-13.53,-6.47]
Van Merode 1989	29	0	-10 (3)		2.41%	-10[-15.88,-4.12]
Gostick 1977	84	0	-9.4 (1.73)		7.25%	-9.4[-12.79,-6.01]
Williams 1992	74	24	-8.2 (4.7)		0.98%	-8.2[-17.41,1.01]
Bengtsson 1976	24	0	-8 (3.86)		1.46%	-8[-15.57,-0.43]
Tonkin 1990	15	0	-8 (4.1)		1.29%	-8[-16.04,0.04]
Broekman 1992	13	0	-8 (5.3)		0.77%	-8[-18.39,2.39]
Frishman 1995	151	75	-7.1 (1.87)		6.21%	-7.1[-10.77,-3.43]
Van Nueten 1997	86	84	-6.9 (2.13)		4.79%	-6.9[-11.07,-2.73]
Papademetriou 2006	95	152	-5.8 (1.77)		6.93%	-5.85[-9.32,-2.38]
Davidov 1994	59	60	-5.3 (2.55)		3.34%	-5.3[-10.3,-0.3]
Weiss 2007	165	81	-5.2 (1.63)		8.17%	-5.2[-8.39,-2.01]
NEB-305	244	75	-4.2 (1.73)		7.25%	-4.2[-7.59,-0.81]
Chrysant 1992	42	43	-4 (2.83)		2.71%	-4[-9.55,1.55]
Frishman 2006	44	95	-2.4 (2.96)		2.48%	-2.4[-8.2,3.4]
Saunders 2007	41	41	-2.3 (3.69)		1.59%	-2.3[-9.53,4.93]
Vanhees 1991	14	0	-1 (4.24)		1.21%	-1[-9.31,7.31]
Subtotal (95% CI)					**100%**	**-9.29[-10.21,-8.38]**
Heterogeneity: Tau²=0; Chi²=104.44, df=31(P<0.0001); I²=70.32%						
Test for overall effect: Z=19.95(P<0.0001)						
9.1.4 2 x starting dose						
Bateman 1979	15	0	-27.5 (3.88)		1.3%	-27.5[-35.1,-19.9]
Gudbjornsdottir 1997	7	0	-22 (5.84)		0.57%	-22[-33.45,-10.55]
Lischner 1987	128	0	-21.1 (1.4)		9.99%	-21.1[-23.84,-18.36]
Houston 1990	30	31	-18 (3.46)		1.64%	-18[-24.78,-11.22]
Hansson 1975	21	23	-17.8 (4.34)		1.04%	-17.8[-26.31,-9.29]
Verdecchia 1983	20	0	-15.7 (3.49)		1.61%	-15.7[-22.54,-8.86]
Jeffers 1977	21	0	-15.3 (2.95)		2.25%	-15.3[-21.08,-9.52]
Myers 1983	12	0	-14 (5)		0.78%	-14[-23.8,-4.2]
Petrie 1980	23	0	-13.3 (3.51)		1.59%	-13.3[-20.18,-6.42]
Lacourciere 1994	19	14	-13.1 (4.9)		0.82%	-13.13[-22.73,-3.53]
Rosen 1994	21	0	-11.9 (3.46)		1.64%	-11.9[-18.68,-5.12]
Ameling 1991	331	0	-11.8 (1.1)		16.18%	-11.8[-13.96,-9.64]
Gostick 1977	84	0	-11.7 (1.73)		6.54%	-11.7[-15.09,-8.31]
Verdecchia 1988	12	0	-11.6 (4.07)		1.18%	-11.6[-19.58,-3.62]
Cilliers 1979	50	0	-11.4 (2.7)		2.69%	-11.4[-16.69,-6.11]
Asmar 1991	14	0	-11 (3.74)		1.4%	-11[-18.33,-3.67]
Ades 1990	10	10	-11 (6.92)		0.41%	-11[-24.56,2.56]

Favour beta blocker -20 -10 0 10 20 Favour placebo

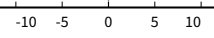
Study or subgroup	Beta blockers N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Papademetriou 2006	51	152	-10.2 (2.19)		4.08%	-10.25[-14.54,-5.96]
Lepantalo 1983	34	0	-8.9 (2.68)		2.73%	-8.9[-14.15,-3.65]
Williams 1992	74	24	-8.6 (4.7)		0.89%	-8.6[-17.81,0.61]
Giles 2014	552	277	-7 (1.1)		16.18%	-7[-9.16,-4.84]
Saunders 2007	47	41	-6.6 (3.08)		2.06%	-6.6[-12.64,-0.56]
Weiss 2007	166	81	-6 (1.7)		6.77%	-6[-9.33,-2.67]
Van Nueten 1997	84	84	-5.6 (2.14)		4.28%	-5.6[-9.79,-1.41]
Davidov 1994	60	60	-5.3 (2.47)		3.21%	-5.3[-10.14,-0.46]
NEB-305	244	75	-2.8 (1.76)		6.32%	-2.8[-6.25,0.65]
Seedat 1980	24	0	1.5 (3.24)		1.87%	1.5[-4.85,7.85]
Subtotal (95% CI)					**100%**	**-10.58[-11.45,-9.71]**
Heterogeneity: Tau²=0; Chi²=158.23, df=26(P<0.0001); I²=83.57%						
Test for overall effect: Z=23.91(P<0.0001)						
9.1.5 4 x starting dose						
Van Herwaarden 1977	8	0	-21 (5)		2.54%	-21[-30.8,-11.2]
Wing 1988	16	0	-16 (3.97)		4.04%	-16[-23.78,-8.22]
Gostick 1977	84	0	-10.7 (1.73)		21.25%	-10.7[-14.09,-7.31]
Jeffers 1977	21	0	-10.4 (2.95)		7.31%	-10.4[-16.18,-4.62]
Saunders 2007	45	41	-8.4 (3.42)		5.44%	-8.4[-15.1,-1.7]
Frishman 2006	90	95	-8.2 (2.59)		9.48%	-8.2[-13.28,-3.12]
Davidov 1994	61	60	-7.6 (2.55)		9.78%	-7.6[-12.6,-2.6]
Weiss 2007	166	81	-6.8 (1.78)		20.08%	-6.8[-10.29,-3.31]
NEB-305	244	75	-6.7 (1.78)		20.08%	-6.7[-10.19,-3.21]
Subtotal (95% CI)					**100%**	**-8.9[-10.47,-7.34]**
Heterogeneity: Tau²=0; Chi²=13.67, df=8(P=0.09); I²=41.48%						
Test for overall effect: Z=11.16(P<0.0001)						
9.1.6 8 x starting dose						
Weiss 2007	166	81	-8.9 (1.69)		79.02%	-8.9[-12.21,-5.59]
Saunders 2007	43	41	-6 (3.28)		20.98%	-6[-12.43,0.43]
Subtotal (95% CI)					**100%**	**-8.29[-11.24,-5.35]**
Heterogeneity: Tau²=0; Chi²=0.62, df=1(P=0.43); I²=0%						
Test for overall effect: Z=5.52(P<0.0001)						
Test for subgroup differences: Chi²=38.3, df=1 (P<0.0001), I²=86.94%						



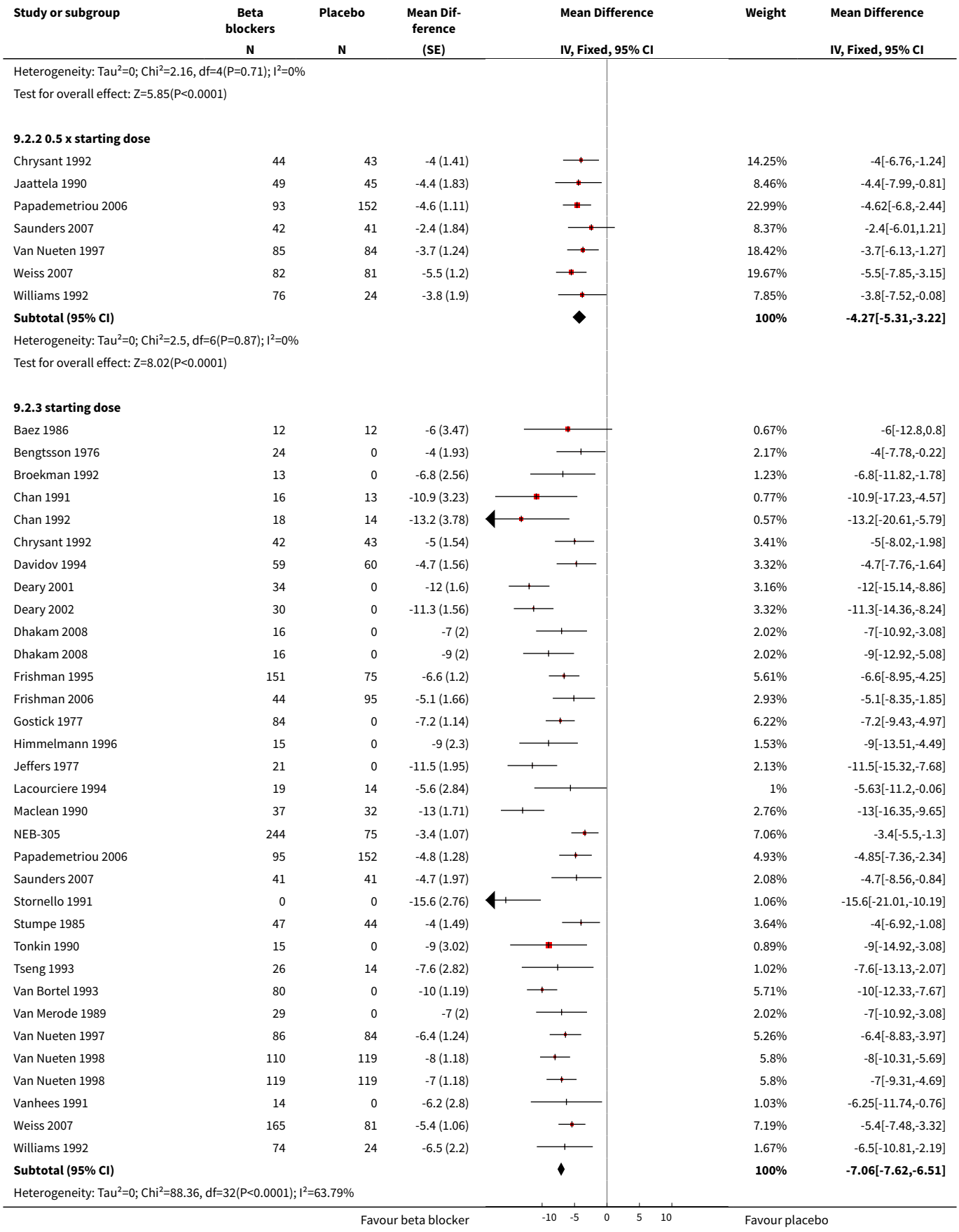
Favour beta blocker | Favour placebo

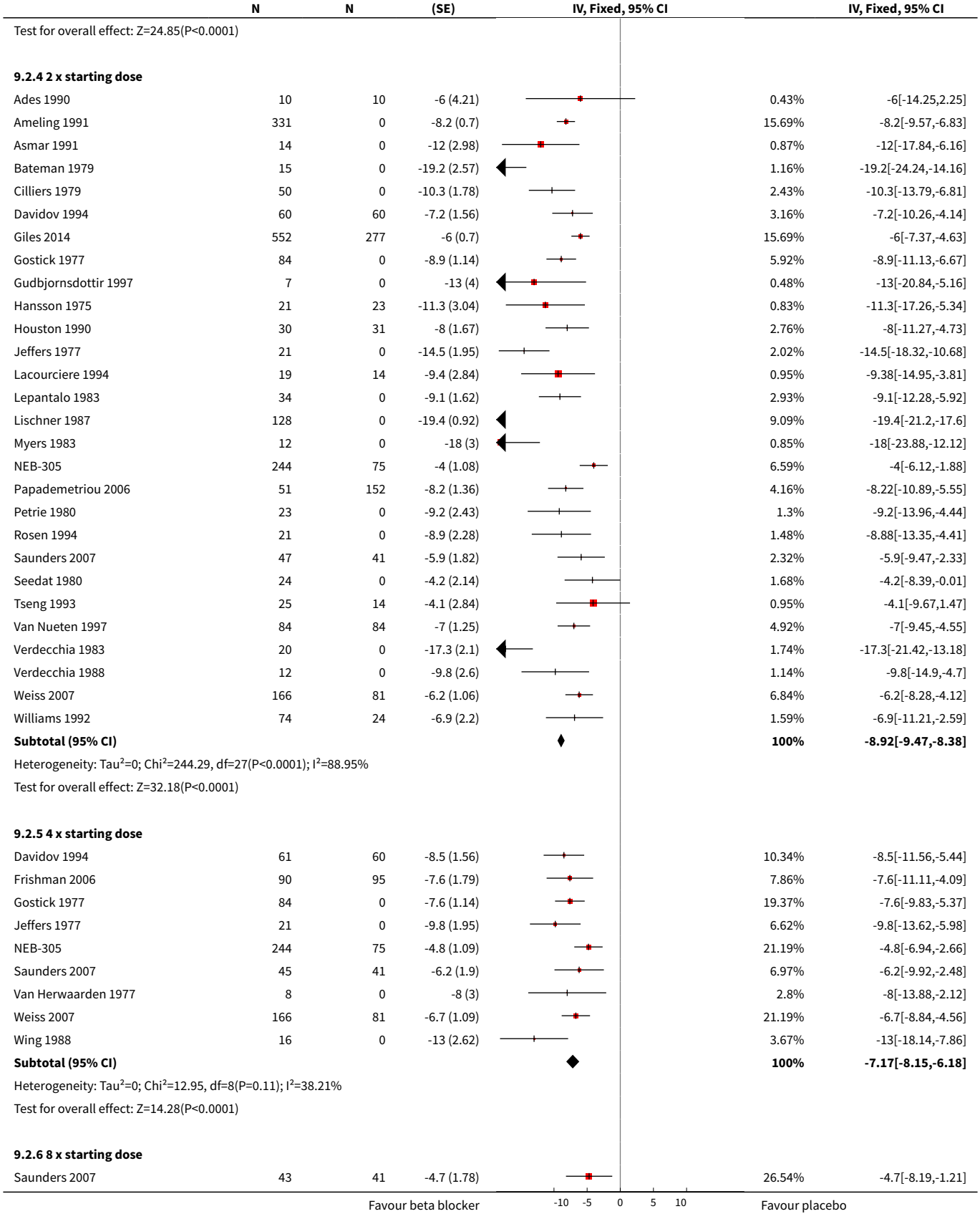
Analysis 9.2. Comparison 9 Pooled overall effect, Outcome 2 DBP.

Study or subgroup	Beta blockers N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
9.2.1 0.25 x starting dose						
Frishman 2006	88	95	-4 (1.57)		15.3%	-4[-7.08,-0.92]
Lacourciere 1994	17	14	-2.5 (2.91)		4.45%	-2.5[-8.2,3.2]
Papademetriou 2006	89	152	-3.5 (1.13)		29.53%	-3.46[-5.67,-1.25]
Van Nueten 1997	87	84	-2.4 (1.24)		24.53%	-2.4[-4.83,0.03]
Weiss 2007	83	81	-4.8 (1.2)		26.19%	-4.8[-7.15,-2.45]
Subtotal (95% CI)					**100%**	**-3.59[-4.79,-2.39]**



Favour beta blocker | Favour placebo





Study or subgroup	Beta blockers N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Test for overall effect: Z=24.85(P<0.0001)						
9.2.4 2 x starting dose						
Ades 1990	10	10	-6 (4.21)		0.43%	-6[-14.25,2.25]
Ameling 1991	331	0	-8.2 (0.7)		15.69%	-8.2[-9.57,-6.83]
Asmar 1991	14	0	-12 (2.98)		0.87%	-12[-17.84,-6.16]
Bateman 1979	15	0	-19.2 (2.57)		1.16%	-19.2[-24.24,-14.16]
Cilliers 1979	50	0	-10.3 (1.78)		2.43%	-10.3[-13.79,-6.81]
Davidov 1994	60	60	-7.2 (1.56)		3.16%	-7.2[-10.26,-4.14]
Giles 2014	552	277	-6 (0.7)		15.69%	-6[-7.37,-4.63]
Gostick 1977	84	0	-8.9 (1.14)		5.92%	-8.9[-11.13,-6.67]
Gudbjornsdottir 1997	7	0	-13 (4)		0.48%	-13[-20.84,-5.16]
Hansson 1975	21	23	-11.3 (3.04)		0.83%	-11.3[-17.26,-5.34]
Houston 1990	30	31	-8 (1.67)		2.76%	-8[-11.27,-4.73]
Jeffers 1977	21	0	-14.5 (1.95)		2.02%	-14.5[-18.32,-10.68]
Lacourciere 1994	19	14	-9.4 (2.84)		0.95%	-9.38[-14.95,-3.81]
Lepantalo 1983	34	0	-9.1 (1.62)		2.93%	-9.1[-12.28,-5.92]
Lischner 1987	128	0	-19.4 (0.92)		9.09%	-19.4[-21.2,-17.6]
Myers 1983	12	0	-18 (3)		0.85%	-18[-23.88,-12.12]
NEB-305	244	75	-4 (1.08)		6.59%	-4[-6.12,-1.88]
Papademetriou 2006	51	152	-8.2 (1.36)		4.16%	-8.22[-10.89,-5.55]
Petrie 1980	23	0	-9.2 (2.43)		1.3%	-9.2[-13.96,-4.44]
Rosen 1994	21	0	-8.9 (2.28)		1.48%	-8.88[-13.35,-4.41]
Saunders 2007	47	41	-5.9 (1.82)		2.32%	-5.9[-9.47,-2.33]
Seedat 1980	24	0	-4.2 (2.14)		1.68%	-4.2[-8.39,-0.01]
Tseng 1993	25	14	-4.1 (2.84)		0.95%	-4.1[-9.67,1.47]
Van Nueten 1997	84	84	-7 (1.25)		4.92%	-7[-9.45,-4.55]
Verdecchia 1983	20	0	-17.3 (2.1)		1.74%	-17.3[-21.42,-13.18]
Verdecchia 1988	12	0	-9.8 (2.6)		1.14%	-9.8[-14.9,-4.7]
Weiss 2007	166	81	-6.2 (1.06)		6.84%	-6.2[-8.28,-4.12]
Williams 1992	74	24	-6.9 (2.2)		1.59%	-6.9[-11.21,-2.59]
Subtotal (95% CI)					**100%**	**-8.92[-9.47,-8.38]**
Heterogeneity: Tau²=0; Chi²=244.29, df=27(P<0.0001); I²=88.95%						
Test for overall effect: Z=32.18(P<0.0001)						
9.2.5 4 x starting dose						
Davidov 1994	61	60	-8.5 (1.56)		10.34%	-8.5[-11.56,-5.44]
Frishman 2006	90	95	-7.6 (1.79)		7.86%	-7.6[-11.11,-4.09]
Gostick 1977	84	0	-7.6 (1.14)		19.37%	-7.6[-9.83,-5.37]
Jeffers 1977	21	0	-9.8 (1.95)		6.62%	-9.8[-13.62,-5.98]
NEB-305	244	75	-4.8 (1.09)		21.19%	-4.8[-6.94,-2.66]
Saunders 2007	45	41	-6.2 (1.9)		6.97%	-6.2[-9.92,-2.48]
Van Herwaarden 1977	8	0	-8 (3)		2.8%	-8[-13.88,-2.12]
Weiss 2007	166	81	-6.7 (1.09)		21.19%	-6.7[-8.84,-4.56]
Wing 1988	16	0	-13 (2.62)		3.67%	-13[-18.14,-7.86]
Subtotal (95% CI)					**100%**	**-7.17[-8.15,-6.18]**
Heterogeneity: Tau²=0; Chi²=12.95, df=8(P=0.11); I²=38.21%						
Test for overall effect: Z=14.28(P<0.0001)						
9.2.6 8 x starting dose						
Saunders 2007	43	41	-4.7 (1.78)		26.54%	-4.7[-8.19,-1.21]

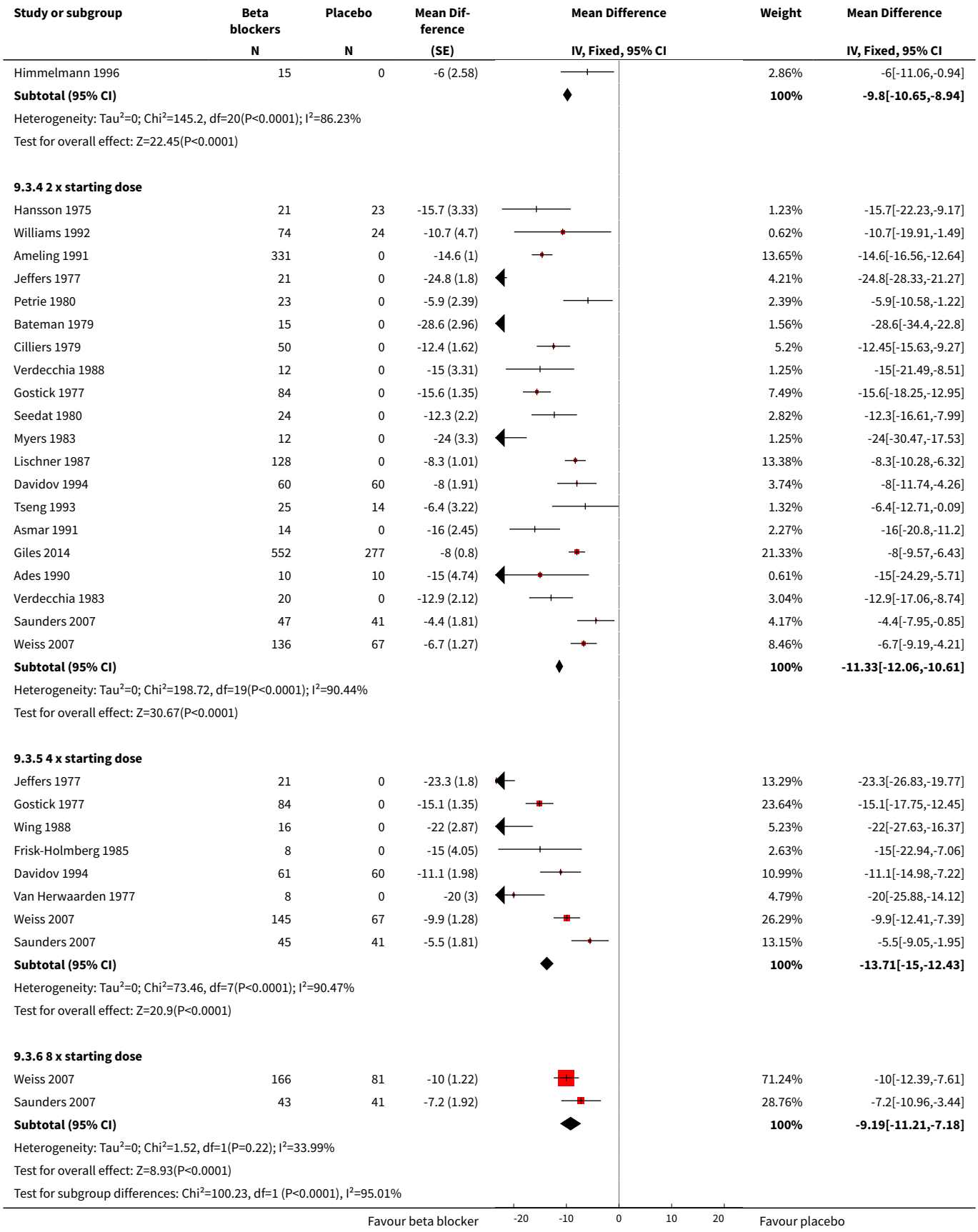
Study or subgroup	Beta blockers N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Weiss 2007	166	81	-8.1 (1.07)		73.46%	-8.1[-10.2,-6]
Subtotal (95% CI)					**100%**	**-7.2[-8.99,-5.4]**
Heterogeneity: Tau²=0; Chi²=2.68, df=1(P=0.1); I²=62.69%						
Test for overall effect: Z=7.85(P<0.0001)						
Test for subgroup differences: Chi²=103.8, df=1 (P<0.0001), I²=95.18%						

Favour beta blocker -10 -5 0 5 10 Favour placebo

Analysis 9.3. Comparison 9 Pooled overall effect, Outcome 3 Heart rate.

Study or subgroup	Beta blockers N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
9.3.1 0.25 x starting dose						
Weiss 2007	69	67	-2.9 (1.51)		100%	-2.9[-5.86,0.06]
Subtotal (95% CI)					**100%**	**-2.9[-5.86,0.06]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.92(P=0.05)						
9.3.2 0.5 x starting dose						
Williams 1992	76	24	-7.4 (4.9)		3.78%	-7.4[-17,2.2]
Chrysant 1992	44	43	-4 (2.83)		11.34%	-4[-9.55,1.55]
Jaattela 1990	49	45	-5.6 (2.26)		17.78%	-5.6[-10.03,-1.17]
Weiss 2007	68	67	-4.5 (1.45)		43.2%	-4.5[-7.34,-1.66]
Saunders 2007	42	41	-2.8 (1.95)		23.89%	-2.8[-6.62,1.02]
Subtotal (95% CI)					**100%**	**-4.34[-6.21,-2.47]**
Heterogeneity: Tau²=0; Chi²=1.35, df=4(P=0.85); I²=0%						
Test for overall effect: Z=4.56(P<0.0001)						
9.3.3 starting dose						
Dhakam 2008	0	0	-19 (2.65)		2.71%	-19[-24.19,-13.81]
Van Nueten 1998	119	119	-7.7 (1.17)		13.9%	-7.7[-9.99,-5.41]
Chrysant 1992	42	43	-3 (2.83)		2.38%	-3[-8.55,2.55]
Williams 1992	74	24	-8.2 (4.7)		0.86%	-8.2[-17.41,1.01]
Jeffers 1977	21	0	-17.8 (1.8)		5.87%	-17.8[-21.33,-14.27]
Dhakam 2008	16	0	-23 (2.87)		2.31%	-23[-28.63,-17.37]
Stornello 1991	12	0	-10.6 (2.75)		2.52%	-10.6[-15.99,-5.21]
Gostick 1977	84	0	-13.8 (1.4)		9.71%	-13.8[-16.54,-11.06]
Vanhees 1991	14	0	-15 (2.49)		3.07%	-15[-19.88,-10.12]
Davidov 1994	59	60	-6 (1.98)		4.85%	-6[-9.88,-2.12]
Tseng 1993	26	14	-5 (3.41)		1.64%	-5[-11.68,1.68]
Broekman 1992	13	0	-5.6 (3.65)		1.43%	-5.6[-12.75,1.55]
Deary 2002	30	0	-9.6 (1.84)		5.62%	-9.6[-13.21,-5.99]
Deary 2001	34	0	-6 (1.73)		6.36%	-6[-9.39,-2.61]
Bengtsson 1976	24	0	-15 (2)		4.76%	-15[-18.92,-11.08]
Weiss 2007	148	67	-6.7 (1.3)		11.26%	-6.7[-9.25,-4.15]
Chan 1991	16	13	-10.9 (3.23)		1.82%	-10.9[-17.23,-4.57]
Saunders 2007	41	41	-2.3 (1.78)		6.01%	-2.3[-5.79,1.19]
Chan 1992	18	14	-1.5 (2.27)		3.69%	-1.5[-5.95,2.95]
Van Bortel 1993	114	0	-16 (1.73)		6.36%	-16[-19.39,-12.61]

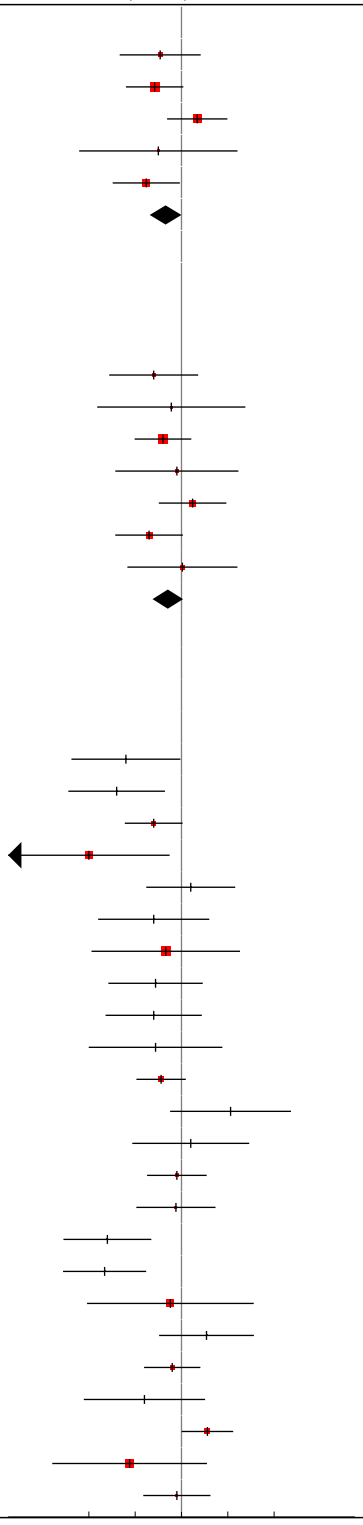
Favour beta blocker -20 -10 0 10 20 Favour placebo

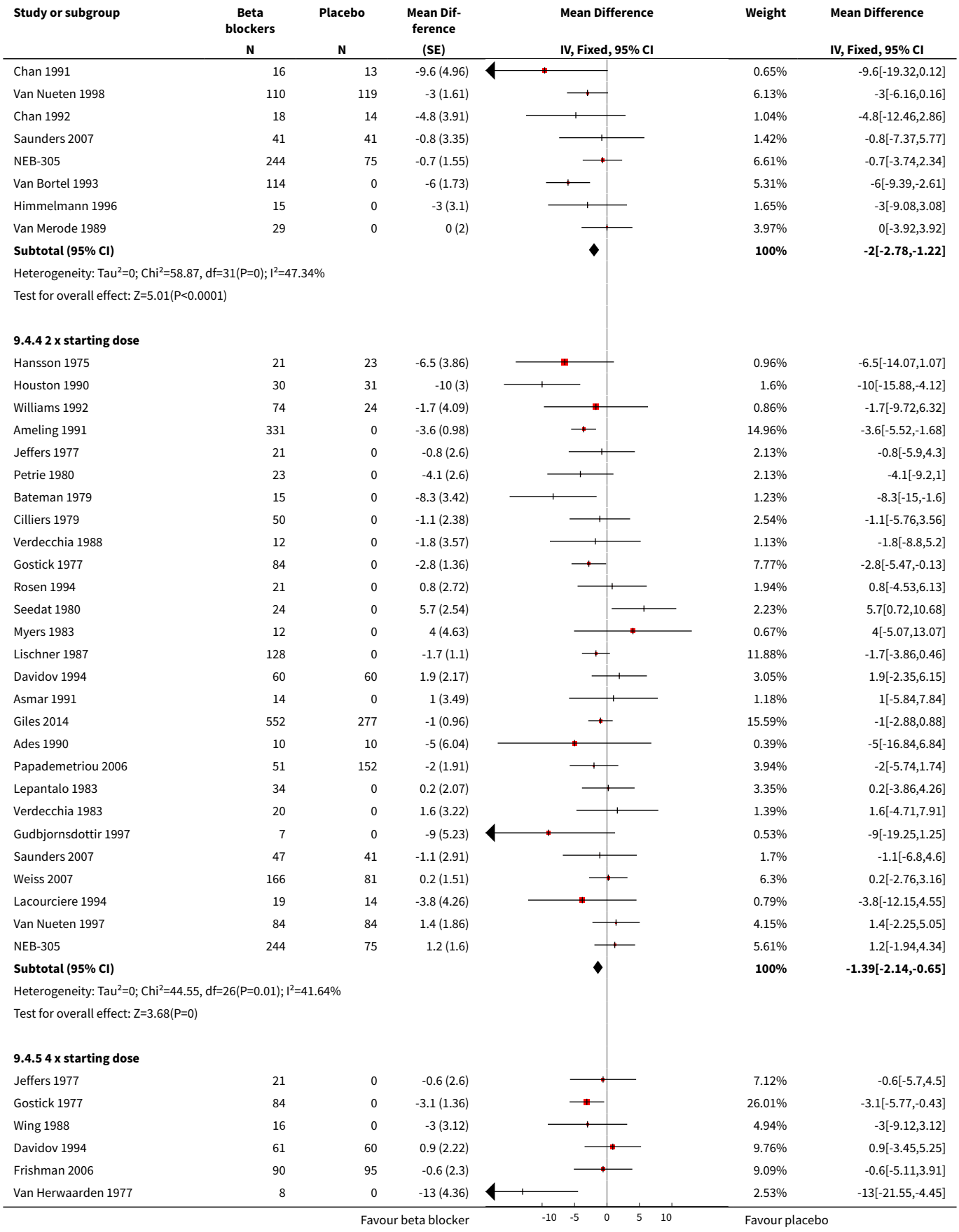


Study or subgroup	Beta blockers N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Himmelmann 1996	15	0	-6 (2.58)		2.86%	-6[-11.06,-0.94]
Subtotal (95% CI)					**100%**	**-9.8[-10.65,-8.94]**
Heterogeneity: Tau²=0; Chi²=145.2, df=20(P<0.0001); I²=86.23%						
Test for overall effect: Z=22.45(P<0.0001)						
9.3.4 2 x starting dose						
Hansson 1975	21	23	-15.7 (3.33)		1.23%	-15.7[-22.23,-9.17]
Williams 1992	74	24	-10.7 (4.7)		0.62%	-10.7[-19.91,-1.49]
Ameling 1991	331	0	-14.6 (1)		13.65%	-14.6[-16.56,-12.64]
Jeffers 1977	21	0	-24.8 (1.8)		4.21%	-24.8[-28.33,-21.27]
Petrie 1980	23	0	-5.9 (2.39)		2.39%	-5.9[-10.58,-1.22]
Bateman 1979	15	0	-28.6 (2.96)		1.56%	-28.6[-34.4,-22.8]
Cilliers 1979	50	0	-12.4 (1.62)		5.2%	-12.45[-15.63,-9.27]
Verdecchia 1988	12	0	-15 (3.31)		1.25%	-15[-21.49,-8.51]
Gostick 1977	84	0	-15.6 (1.35)		7.49%	-15.6[-18.25,-12.95]
Seedat 1980	24	0	-12.3 (2.2)		2.82%	-12.3[-16.61,-7.99]
Myers 1983	12	0	-24 (3.3)		1.25%	-24[-30.47,-17.53]
Lischner 1987	128	0	-8.3 (1.01)		13.38%	-8.3[-10.28,-6.32]
Davidov 1994	60	60	-8 (1.91)		3.74%	-8[-11.74,-4.26]
Tseng 1993	25	14	-6.4 (3.22)		1.32%	-6.4[-12.71,-0.09]
Asmar 1991	14	0	-16 (2.45)		2.27%	-16[-20.8,-11.2]
Giles 2014	552	277	-8 (0.8)		21.33%	-8[-9.57,-6.43]
Ades 1990	10	10	-15 (4.74)		0.61%	-15[-24.29,-5.71]
Verdecchia 1983	20	0	-12.9 (2.12)		3.04%	-12.9[-17.06,-8.74]
Saunders 2007	47	41	-4.4 (1.81)		4.17%	-4.4[-7.95,-0.85]
Weiss 2007	136	67	-6.7 (1.27)		8.46%	-6.7[-9.19,-4.21]
Subtotal (95% CI)					**100%**	**-11.33[-12.06,-10.61]**
Heterogeneity: Tau²=0; Chi²=198.72, df=19(P<0.0001); I²=90.44%						
Test for overall effect: Z=30.67(P<0.0001)						
9.3.5 4 x starting dose						
Jeffers 1977	21	0	-23.3 (1.8)		13.29%	-23.3[-26.83,-19.77]
Gostick 1977	84	0	-15.1 (1.35)		23.64%	-15.1[-17.75,-12.45]
Wing 1988	16	0	-22 (2.87)		5.23%	-22[-27.63,-16.37]
Frisk-Holmberg 1985	8	0	-15 (4.05)		2.63%	-15[-22.94,-7.06]
Davidov 1994	61	60	-11.1 (1.98)		10.99%	-11.1[-14.98,-7.22]
Van Herwaarden 1977	8	0	-20 (3)		4.79%	-20[-25.88,-14.12]
Weiss 2007	145	67	-9.9 (1.28)		26.29%	-9.9[-12.41,-7.39]
Saunders 2007	45	41	-5.5 (1.81)		13.15%	-5.5[-9.05,-1.95]
Subtotal (95% CI)					**100%**	**-13.71[-15,-12.43]**
Heterogeneity: Tau²=0; Chi²=73.46, df=7(P<0.0001); I²=90.47%						
Test for overall effect: Z=20.9(P<0.0001)						
9.3.6 8 x starting dose						
Weiss 2007	166	81	-10 (1.22)		71.24%	-10[-12.39,-7.61]
Saunders 2007	43	41	-7.2 (1.92)		28.76%	-7.2[-10.96,-3.44]
Subtotal (95% CI)					**100%**	**-9.19[-11.21,-7.18]**
Heterogeneity: Tau²=0; Chi²=1.52, df=1(P=0.22); I²=33.99%						
Test for overall effect: Z=8.93(P<0.0001)						
Test for subgroup differences: Chi²=100.23, df=1 (P<0.0001), I²=95.01%						

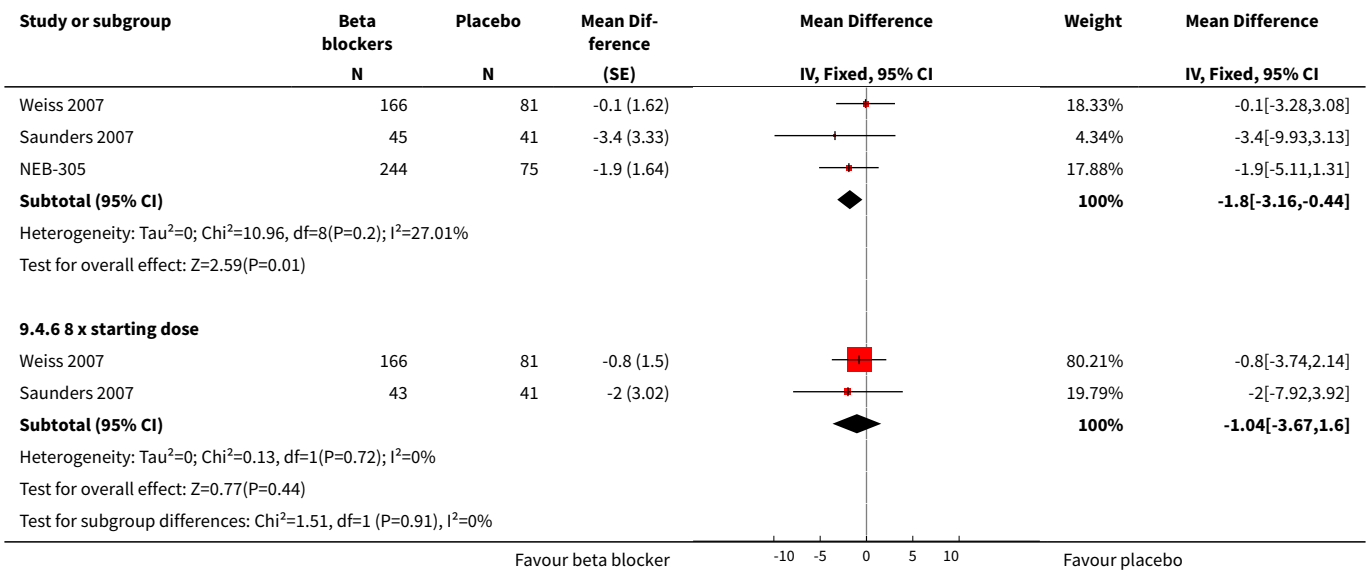
Analysis 9.4. Comparison 9 Pooled overall effect, Outcome 4 Pulse pressure.

Study or subgroup	Beta blockers N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
9.4.1 0.25 x starting dose						
Frishman 2006	88	95	-2.3 (2.23)		15.36%	-2.3[-6.67,2.07]
Papademetriou 2006	89	152	-2.9 (1.58)		30.59%	-2.9[-6,0.2]
Weiss 2007	83	81	1.7 (1.66)		27.72%	1.7[-1.55,4.95]
Lacourciere 1994	17	14	-2.5 (4.36)		4.02%	-2.5[-11.05,6.05]
Van Nueten 1997	87	84	-3.8 (1.85)		22.32%	-3.8[-7.43,-0.17]
Subtotal (95% CI)					**100%**	**-1.72[-3.43,-0]**
Heterogeneity: Tau^2=0; Chi^2=6.17, df=4(P=0.19); I^2=35.13%						
Test for overall effect: Z=1.97(P=0.05)						
9.4.2 0.5 x starting dose						
Chrysant 1992	44	43	-3 (2.45)		11.8%	-3[-7.8,1.8]
Williams 1992	76	24	-1.1 (4.08)		4.26%	-1.1[-9.1,6.9]
Papademetriou 2006	93	152	-2 (1.56)		29.11%	-2[-5.06,1.06]
Jaattela 1990	49	45	-0.5 (3.39)		6.16%	-0.5[-7.14,6.14]
Weiss 2007	82	81	1.2 (1.86)		20.48%	1.2[-2.45,4.85]
Van Nueten 1997	85	84	-3.5 (1.86)		20.48%	-3.5[-7.15,0.15]
Saunders 2007	42	41	0.1 (3.03)		7.72%	0.1[-5.84,6.04]
Subtotal (95% CI)					**100%**	**-1.48[-3.13,0.17]**
Heterogeneity: Tau^2=0; Chi^2=4.12, df=6(P=0.66); I^2=0%						
Test for overall effect: Z=1.75(P=0.08)						
9.4.3 starting dose						
Dhakam 2008	16	0	-6 (3)		1.76%	-6[-11.88,-0.12]
Stumpe 1985	47	44	-7 (2.66)		2.24%	-7[-12.21,-1.79]
Van Nueten 1998	119	119	-3 (1.59)		6.28%	-3[-6.12,0.12]
Baez 1986	12	12	-10 (4.45)		0.8%	-10[-18.72,-1.28]
Chrysant 1992	42	43	1 (2.45)		2.65%	1[-3.8,5.8]
Maclean 1990	37	32	-3 (3.06)		1.7%	-3[-9,3]
Williams 1992	74	24	-1.7 (4.09)		0.95%	-1.7[-9.72,6.32]
Jeffers 1977	21	0	-2.8 (2.6)		2.35%	-2.8[-7.9,2.3]
Dhakam 2008	16	0	-3 (2.65)		2.26%	-3[-8.19,2.19]
Stornello 1991	12	0	-2.8 (3.68)		1.17%	-2.8[-10.01,4.41]
Gostick 1977	84	0	-2.2 (1.36)		8.59%	-2.2[-4.87,0.47]
Vanhees 1991	14	0	5.3 (3.33)		1.43%	5.3[-1.23,11.83]
Tonkin 1990	15	0	1 (3.22)		1.53%	1[-5.31,7.31]
Frishman 1995	151	75	-0.5 (1.64)		5.91%	-0.5[-3.71,2.71]
Davidov 1994	59	60	-0.6 (2.18)		3.34%	-0.6[-4.87,3.67]
Deary 2001	34	0	-8 (2.42)		2.71%	-8[-12.74,-3.26]
Deary 2002	30	0	-8.3 (2.29)		3.03%	-8.3[-12.79,-3.81]
Broekman 1992	13	0	-1.2 (4.59)		0.75%	-1.2[-10.2,7.8]
Frishman 2006	44	95	2.7 (2.61)		2.33%	2.7[-2.42,7.82]
Papademetriou 2006	95	152	-1 (1.55)		6.61%	-1[-4.04,2.04]
Bengtsson 1976	24	0	-4 (3.34)		1.42%	-4[-10.55,2.55]
Weiss 2007	165	81	2.8 (1.42)		7.88%	2.8[0.02,5.58]
Lacourciere 1994	19	14	-5.6 (4.26)		0.88%	-5.6[-13.95,2.75]
Van Nueten 1997	86	84	-0.5 (1.85)		4.64%	-0.5[-4.13,3.13]

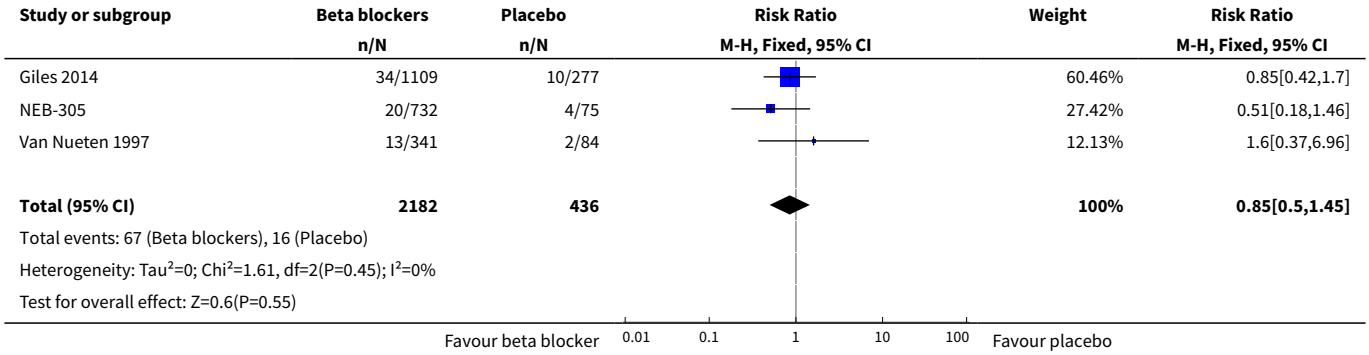




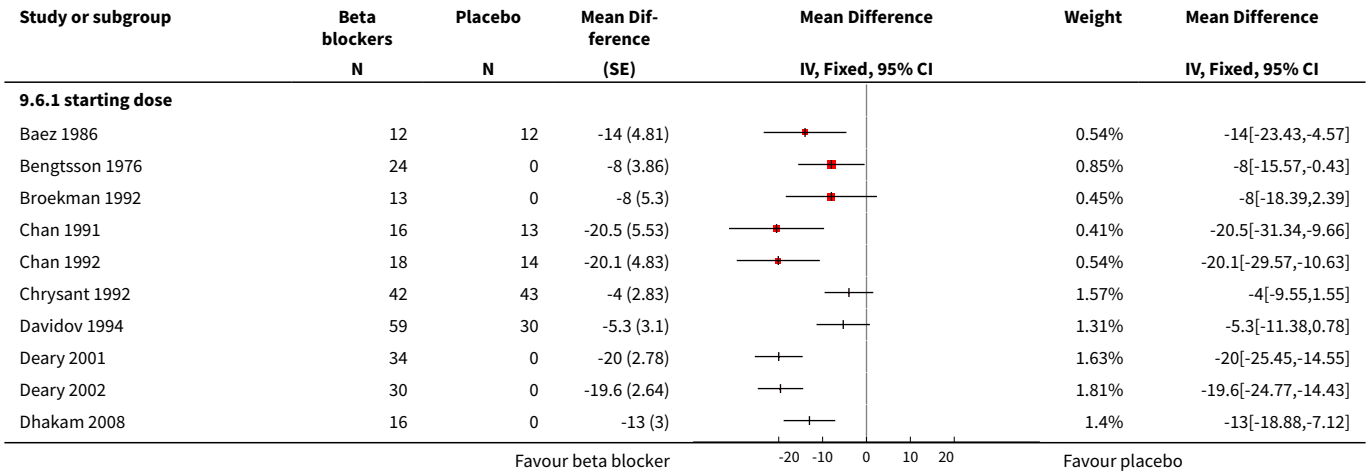
Study or subgroup	Beta blockers N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Chan 1991	16	13	-9.6 (4.96)		0.65%	-9.6[-19.32,0.12]
Van Nueten 1998	110	119	-3 (1.61)		6.13%	-3[-6.16,0.16]
Chan 1992	18	14	-4.8 (3.91)		1.04%	-4.8[-12.46,2.86]
Saunders 2007	41	41	-0.8 (3.35)		1.42%	-0.8[-7.37,5.77]
NEB-305	244	75	-0.7 (1.55)		6.61%	-0.7[-3.74,2.34]
Van Bortel 1993	114	0	-6 (1.73)		5.31%	-6[-9.39,-2.61]
Himmelmann 1996	15	0	-3 (3.1)		1.65%	-3[-9.08,3.08]
Van Merode 1989	29	0	0 (2)		3.97%	0[-3.92,3.92]
Subtotal (95% CI)					**100%**	**-2[-2.78,-1.22]**
Heterogeneity: Tau²=0; Chi²=58.87, df=31(P=0); I²=47.34%						
Test for overall effect: Z=5.01(P<0.0001)						
9.4.4 2 x starting dose						
Hansson 1975	21	23	-6.5 (3.86)		0.96%	-6.5[-14.07,1.07]
Houston 1990	30	31	-10 (3)		1.6%	-10[-15.88,-4.12]
Williams 1992	74	24	-1.7 (4.09)		0.86%	-1.7[-9.72,6.32]
Ameling 1991	331	0	-3.6 (0.98)		14.96%	-3.6[-5.52,-1.68]
Jeffers 1977	21	0	-0.8 (2.6)		2.13%	-0.8[-5.9,4.3]
Petrie 1980	23	0	-4.1 (2.6)		2.13%	-4.1[-9.2,1]
Bateman 1979	15	0	-8.3 (3.42)		1.23%	-8.3[-15,-1.6]
Cilliers 1979	50	0	-1.1 (2.38)		2.54%	-1.1[-5.76,3.56]
Verdecchia 1988	12	0	-1.8 (3.57)		1.13%	-1.8[-8.8,5.2]
Gostick 1977	84	0	-2.8 (1.36)		7.77%	-2.8[-5.47,-0.13]
Rosen 1994	21	0	0.8 (2.72)		1.94%	0.8[-4.53,6.13]
Seedat 1980	24	0	5.7 (2.54)		2.23%	5.7[0.72,10.68]
Myers 1983	12	0	4 (4.63)		0.67%	4[-5.07,13.07]
Lischner 1987	128	0	-1.7 (1.1)		11.88%	-1.7[-3.86,0.46]
Davidov 1994	60	60	1.9 (2.17)		3.05%	1.9[-2.35,6.15]
Asmar 1991	14	0	1 (3.49)		1.18%	1[-5.84,7.84]
Giles 2014	552	277	-1 (0.96)		15.59%	-1[-2.88,0.88]
Ades 1990	10	10	-5 (6.04)		0.39%	-5[-16.84,6.84]
Papademetriou 2006	51	152	-2 (1.91)		3.94%	-2[-5.74,1.74]
Lepantalo 1983	34	0	0.2 (2.07)		3.35%	0.2[-3.86,4.26]
Verdecchia 1983	20	0	1.6 (3.22)		1.39%	1.6[-4.71,7.91]
Gudbjornsdottir 1997	7	0	-9 (5.23)		0.53%	-9[-19.25,1.25]
Saunders 2007	47	41	-1.1 (2.91)		1.7%	-1.1[-6.8,4.6]
Weiss 2007	166	81	0.2 (1.51)		6.3%	0.2[-2.76,3.16]
Lacourciere 1994	19	14	-3.8 (4.26)		0.79%	-3.8[-12.15,4.55]
Van Nueten 1997	84	84	1.4 (1.86)		4.15%	1.4[-2.25,5.05]
NEB-305	244	75	1.2 (1.6)		5.61%	1.2[-1.94,4.34]
Subtotal (95% CI)					**100%**	**-1.39[-2.14,-0.65]**
Heterogeneity: Tau²=0; Chi²=44.55, df=26(P=0.01); I²=41.64%						
Test for overall effect: Z=3.68(P=0)						
9.4.5 4 x starting dose						
Jeffers 1977	21	0	-0.6 (2.6)		7.12%	-0.6[-5.7,4.5]
Gostick 1977	84	0	-3.1 (1.36)		26.01%	-3.1[-5.77,-0.43]
Wing 1988	16	0	-3 (3.12)		4.94%	-3[-9.12,3.12]
Davidov 1994	61	60	0.9 (2.22)		9.76%	0.9[-3.45,5.25]
Frishman 2006	90	95	-0.6 (2.3)		9.09%	-0.6[-5.11,3.91]
Van Herwaarden 1977	8	0	-13 (4.36)		2.53%	-13[-21.55,-4.45]

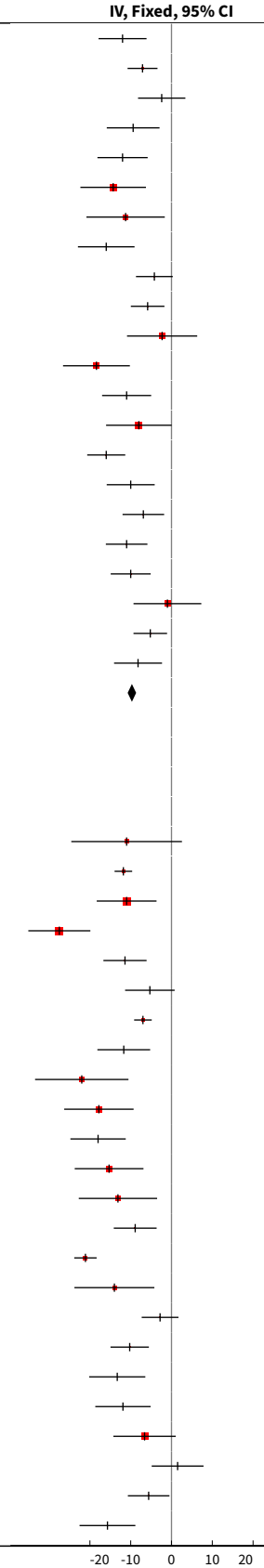


Analysis 9.5. Comparison 9 Pooled overall effect, Outcome 5 WDAE.



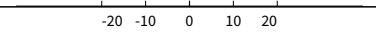
Analysis 9.6. Comparison 9 Pooled overall effect, Outcome 6 SBP combined starting dose and 2 x starting dose.





Study or subgroup	Beta blockers N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Dhakam 2008	16	0	-12 (3)		1.4%	-12[-17.88,-6.12]
Frishman 1995	151	75	-7.1 (1.87)		3.6%	-7.1[-10.77,-3.43]
Frishman 2006	44	95	-2.4 (2.96)		1.44%	-2.4[-8.2,3.4]
Gostick 1977	42	0	-9.4 (3.3)		1.16%	-9.4[-15.87,-2.93]
Himmelmann 1996	15	0	-12 (3.14)		1.28%	-12[-18.15,-5.85]
Jeffers 1977	11	0	-14.3 (4.1)		0.75%	-14.3[-22.34,-6.26]
Lacourciere 1994	19	14	-11.2 (4.9)		0.52%	-11.25[-20.85,-1.65]
Maclean 1990	37	32	-16 (3.54)		1.01%	-16[-22.94,-9.06]
NEB-305	244	38	-4.2 (2.3)		2.38%	-4.2[-8.71,0.31]
Papademetriou 2006	95	76	-5.8 (2.1)		2.86%	-5.85[-9.97,-1.73]
Saunders 2007	41	21	-2.3 (4.39)		0.65%	-2.3[-10.9,6.3]
Stornello 1991	12	0	-18.4 (4.18)		0.72%	-18.4[-26.59,-10.21]
Stumpe 1985	47	44	-11 (3.07)		1.34%	-11[-17.02,-4.98]
Tonkin 1990	15	0	-8 (4.1)		0.75%	-8[-16.04,0.04]
Van Bortel 1993	114	0	-16 (2.38)		2.22%	-16[-20.66,-11.34]
Van Merode 1989	29	0	-10 (3)		1.4%	-10[-15.88,-4.12]
Van Nueten 1997	86	42	-6.9 (2.6)		1.86%	-6.9[-12,-1.8]
Van Nueten 1998	110	60	-11 (2.6)		1.86%	-11[-16.1,-5.9]
Van Nueten 1998	119	59	-10 (2.5)		2.02%	-10[-14.9,-5.1]
Vanhees 1991	14	0	-1 (4.24)		0.7%	-1[-9.31,7.31]
Weiss 2007	165	41	-5.2 (2.1)		2.86%	-5.2[-9.32,-1.08]
Williams 1992	74	36	-8.2 (3)		1.4%	-8.2[-14.08,-2.32]
Subtotal (95% CI)					**44.68%**	**-9.71[-10.75,-8.67]**
Heterogeneity: Tau²=0; Chi²=92.39, df=31(P<0.0001); I²=66.45%						
Test for overall effect: Z=18.28(P<0.0001)						
9.6.2 2 x starting dose						
Ades 1990	10	10	-11 (6.92)		0.26%	-11[-24.56,2.56]
Ameling 1991	331	0	-11.8 (1.1)		10.41%	-11.8[-13.96,-9.64]
Asmar 1991	14	0	-11 (3.74)		0.9%	-11[-18.33,-3.67]
Bateman 1979	15	0	-27.5 (3.88)		0.84%	-27.5[-35.1,-19.9]
Cilliers 1979	50	0	-11.4 (2.7)		1.73%	-11.4[-16.69,-6.11]
Davidov 1994	60	30	-5.3 (3.1)		1.31%	-5.3[-11.38,0.78]
Giles 2014	552	277	-7 (1.1)		10.41%	-7[-9.16,-4.84]
Gostick 1977	42	0	-11.7 (3.3)		1.16%	-11.7[-18.17,-5.23]
Gudbjornsdottir 1997	7	0	-22 (5.84)		0.37%	-22[-33.45,-10.55]
Hansson 1975	21	23	-17.8 (4.34)		0.67%	-17.8[-26.31,-9.29]
Houston 1990	30	31	-18 (3.46)		1.05%	-18[-24.78,-11.22]
Jeffers 1977	10	0	-15.3 (4.3)		0.68%	-15.3[-23.73,-6.87]
Lacourciere 1994	19	14	-13.1 (4.9)		0.52%	-13.13[-22.73,-3.53]
Lepantalo 1983	34	0	-8.9 (2.68)		1.75%	-8.9[-14.15,-3.65]
Lischner 1987	128	0	-21.1 (1.4)		6.43%	-21.1[-23.84,-18.36]
Myers 1983	12	0	-14 (5)		0.5%	-14[-23.8,-4.2]
NEB-305	244	37	-2.8 (2.3)		2.38%	-2.8[-7.31,1.71]
Papademetriou 2006	51	76	-10.2 (2.4)		2.19%	-10.25[-14.95,-5.55]
Petrie 1980	23	0	-13.3 (3.51)		1.02%	-13.3[-20.18,-6.42]
Rosen 1994	21	0	-11.9 (3.46)		1.05%	-11.9[-18.68,-5.12]
Saunders 2007	47	20	-6.6 (3.9)		0.83%	-6.6[-14.24,1.04]
Seedat 1980	24	0	1.5 (3.24)		1.2%	1.5[-4.85,7.85]
Van Nueten 1997	84	42	-5.6 (2.6)		1.86%	-5.6[-10.7,-0.5]
Verdecchia 1983	20	0	-15.7 (3.49)		1.03%	-15.7[-22.54,-8.86]

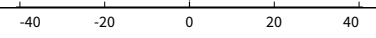
Study or subgroup	Beta blockers N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Verdecchia 1988	12	0	-11.6 (4.07)		0.76%	-11.6[-19.58,-3.62]
Weiss 2007	166	40	-6 (2.2)		2.6%	-6[-10.31,-1.69]
Williams 1992	74	36	-8.6 (3)		1.4%	-8.6[-14.48,-2.72]
Subtotal (95% CI)					**55.32%**	**-10.99[-11.93,-10.06]**
Heterogeneity: Tau^2=0; Chi^2=141.01, df=26(P<0.0001); I^2=81.56%						
Test for overall effect: Z=23.04(P<0.0001)						
Total (95% CI)					**100%**	**-10.42[-11.11,-9.72]**
Heterogeneity: Tau^2=0; Chi^2=236.64, df=58(P<0.0001); I^2=75.49%						
Test for overall effect: Z=29.36(P<0.0001)						
Test for subgroup differences: Chi^2=3.25, df=1 (P=0.07), I^2=69.23%						



Favour beta blocker | Favour placebo

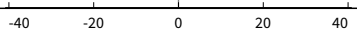
Analysis 9.7. Comparison 9 Pooled overall effect, Outcome 7 DBP combined starting dose and 2 x starting dose.

Study or subgroup	Beta blockers N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
9.7.1 starting dose						
Baez 1986	12	12	-6 (3.47)		0.39%	-6[-12.8,0.8]
Bengtsson 1976	24	0	-4 (1.93)		1.26%	-4[-7.78,-0.22]
Broekman 1992	13	0	-6.8 (2.56)		0.71%	-6.8[-11.82,-1.78]
Chan 1991	16	13	-10.9 (3.23)		0.45%	-10.9[-17.23,-4.57]
Chan 1992	18	14	-13.2 (3.78)		0.33%	-13.2[-20.61,-5.79]
Chrysant 1992	42	43	-5 (1.54)		1.97%	-5[-8.02,-1.98]
Davidov 1994	59	30	-4.7 (1.9)		1.3%	-4.7[-8.42,-0.98]
Deary 2001	34	0	-12 (1.6)		1.83%	-12[-15.14,-8.86]
Deary 2002	30	0	-11.3 (1.56)		1.92%	-11.3[-14.36,-8.24]
Dhakam 2008	16	0	-7 (2)		1.17%	-7[-10.92,-3.08]
Dhakam 2008	16	0	-9 (2)		1.17%	-9[-12.92,-5.08]
Frishman 1995	151	75	-6.6 (1.2)		3.25%	-6.6[-8.95,-4.25]
Frishman 2006	44	95	-5.1 (1.66)		1.7%	-5.1[-8.35,-1.85]
Gostick 1977	42	0	-7.2 (1.7)		1.62%	-7.2[-10.53,-3.87]
Himmelmann 1996	15	0	-9 (2.3)		0.88%	-9[-13.51,-4.49]
Jeffers 1977	11	0	-11.5 (2.7)		0.64%	-11.5[-16.79,-6.21]
Lacourciere 1994	19	14	-5.6 (2.84)		0.58%	-5.63[-11.2,-0.06]
Maclean 1990	37	32	-13 (1.71)		1.6%	-13[-16.35,-9.65]
NEB-305	244	38	-3.4 (1.42)		2.32%	-3.4[-6.18,-0.62]
Papademetriou 2006	95	76	-4.8 (1.3)		2.77%	-4.85[-7.4,-2.3]
Saunders 2007	41	24	-4.7 (2.4)		0.81%	-4.7[-9.4,0]
Stornello 1991	0	0	-15.6 (2.76)		0.61%	-15.6[-21.01,-10.19]
Stumpe 1985	47	44	-4 (1.49)		2.11%	-4[-6.92,-1.08]
Tonkin 1990	15	0	-9 (3.02)		0.51%	-9[-14.92,-3.08]
Tseng 1993	26	14	-7.6 (2.82)		0.59%	-7.6[-13.13,-2.07]
Van Bortel 1993	114	0	-10 (1.19)		3.3%	-10[-12.33,-7.67]
Van Merode 1989	29	0	-7 (2)		1.17%	-7[-10.92,-3.08]
Van Nueten 1997	86	42	-6.4 (1.5)		2.08%	-6.4[-9.34,-3.46]
Van Nueten 1998	119	59	-7 (1.8)		1.44%	-7[-10.53,-3.47]
Van Nueten 1998	110	60	-8 (1.98)		1.19%	-8[-11.88,-4.12]



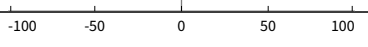
Favour beta blocker | Favour placebo

Study or subgroup	Beta blockers N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Vanhees 1991	14	0	-6.2 (2.8)		0.6%	-6.25[-11.74,-0.76]
Weiss 2007	165	41	-5.4 (1.4)		2.39%	-5.4[-8.14,-2.66]
Williams 1992	74	36	-6.5 (1.7)		1.62%	-6.5[-9.83,-3.17]
Subtotal (95% CI)					**46.28%**	**-7.23[-7.85,-6.6]**
Heterogeneity: Tau²=0; Chi²=77.74, df=32(P<0.0001); I²=58.83%						
Test for overall effect: Z=22.73(P<0.0001)						
9.7.2 2x starting dose						
Ades 1990	10	10	-6 (4.21)		0.26%	-6[-14.25,2.25]
Ameling 1991	331	0	-8.2 (0.7)		9.55%	-8.2[-9.57,-6.83]
Asmar 1991	14	0	-12 (2.98)		0.53%	-12[-17.84,-6.16]
Bateman 1979	15	0	-19.2 (2.57)		0.71%	-19.2[-24.24,-14.16]
Cilliers 1979	50	0	-10.3 (1.78)		1.48%	-10.3[-13.79,-6.81]
Davidov 1994	60	30	-7.2 (1.9)		1.3%	-7.2[-10.92,-3.48]
Giles 2014	552	277	-6 (0.7)		9.55%	-6[-7.37,-4.63]
Gostick 1977	42	0	-8.9 (1.4)		2.39%	-8.9[-11.64,-6.16]
Gudbjornsdottir 1997	7	0	-13 (4)		0.29%	-13[-20.84,-5.16]
Hansson 1975	21	23	-11.3 (3.04)		0.51%	-11.3[-17.26,-5.34]
Houston 1990	30	31	-8 (1.67)		1.68%	-8[-11.27,-4.73]
Jeffers 1977	10	0	-14.5 (2.8)		0.6%	-14.5[-19.99,-9.01]
Lacourciere 1994	19	14	-9.4 (2.84)		0.58%	-9.38[-14.95,-3.81]
Lepantalo 1983	34	0	-9.1 (1.62)		1.78%	-9.1[-12.28,-5.92]
Lischner 1987	128	0	-19.4 (0.92)		5.53%	-19.4[-21.2,-17.6]
Myers 1983	12	0	-18 (3)		0.52%	-18[-23.88,-12.12]
NEB-305	244	37	-4 (1.4)		2.39%	-4[-6.74,-1.26]
Papademetriou 2006	51	76	-8.2 (1.5)		2.08%	-8.22[-11.16,-5.28]
Petrie 1980	23	0	-9.2 (2.43)		0.79%	-9.2[-13.96,-4.44]
Rosen 1994	21	0	-8.9 (2.28)		0.9%	-8.88[-13.35,-4.41]
Saunders 2007	47	20	-5.9 (2.3)		0.88%	-5.9[-10.41,-1.39]
Seedat 1980	24	0	-4.2 (2.14)		1.02%	-4.2[-8.39,-0.01]
Tseng 1993	25	14	-4.1 (2.84)		0.58%	-4.1[-9.67,1.47]
Van Nueten 1997	84	42	-7 (1.5)		2.08%	-7[-9.94,-4.06]
Verdecchia 1983	20	0	-17.3 (2.1)		1.06%	-17.3[-21.42,-13.18]
Verdecchia 1988	12	0	-9.8 (2.6)		0.69%	-9.8[-14.9,-4.7]
Weiss 2007	166	40	-6.2 (1.4)		2.39%	-6.2[-8.94,-3.46]
Williams 1992	74	36	-6.9 (1.7)		1.62%	-6.9[-10.23,-3.57]
Subtotal (95% CI)					**53.72%**	**-9.16[-9.74,-8.58]**
Heterogeneity: Tau²=0; Chi²=226.56, df=27(P<0.0001); I²=88.08%						
Test for overall effect: Z=31.05(P<0.0001)						
Total (95% CI)					**100%**	**-8.27[-8.69,-7.84]**
Heterogeneity: Tau²=0; Chi²=324.19, df=60(P<0.0001); I²=81.49%						
Test for overall effect: Z=38.22(P<0.0001)						
Test for subgroup differences: Chi²=19.9, df=1 (P<0.0001), I²=94.97%						



Analysis 9.8. Comparison 9 Pooled overall effect, Outcome 8 Heart rate combined starting dose and 2 x starting dose.

Study or subgroup	Beta blockers N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
9.8.1 starting dose						
Bengtsson 1976	24	0	-15 (2)		2.03%	-15[-18.92,-11.08]
Broekman 1992	13	0	-5.6 (3.65)		0.61%	-5.6[-12.75,1.55]
Chan 1991	16	13	-10.9 (3.23)		0.78%	-10.9[-17.23,-4.57]
Chan 1992	18	14	-1.5 (2.27)		1.57%	-1.5[-5.95,2.95]
Chrysant 1992	42	43	-3 (2.83)		1.01%	-3[-8.55,2.55]
Davidov 1994	59	30	-6 (2.4)		1.41%	-6[-10.7,-1.3]
Deary 2001	34	0	-6 (1.73)		2.71%	-6[-9.39,-2.61]
Deary 2002	30	0	-9.6 (1.84)		2.4%	-9.6[-13.21,-5.99]
Dhakam 2008	16	0	-23 (2.87)		0.98%	-23[-28.63,-17.37]
Dhakam 2008	0	0	-19 (2.65)		1.15%	-19[-24.19,-13.81]
Gostick 1977	84	0	-13.8 (1.4)		4.14%	-13.8[-16.54,-11.06]
Himmelmann 1996	15	0	-6 (2.58)		1.22%	-6[-11.06,-0.94]
Jeffers 1977	21	0	-17.8 (1.8)		2.5%	-17.8[-21.33,-14.27]
Saunders 2007	41	21	-2.3 (2.2)		1.68%	-2.3[-6.61,2.01]
Stornello 1991	12	0	-10.6 (2.75)		1.07%	-10.6[-15.99,-5.21]
Tseng 1993	26	14	-5 (3.41)		0.7%	-5[-11.68,1.68]
Van Bortel 1993	114	0	-16 (1.73)		2.71%	-16[-19.39,-12.61]
Van Nueten 1998	119	119	-7.7 (1.17)		5.92%	-7.7[-9.99,-5.41]
Vanhees 1991	14	0	-15 (2.49)		1.31%	-15[-19.88,-10.12]
Weiss 2007	165	41	-6.7 (1.5)		3.6%	-6.7[-9.64,-3.76]
Williams 1992	74	36	-8.2 (1.9)		2.25%	-8.2[-11.92,-4.48]
Subtotal (95% CI)					**41.75%**	**-10.03[-10.9,-9.17]**
Heterogeneity: Tau²=0; Chi²=136.8, df=20(P<0.0001); I²=85.38%						
Test for overall effect: Z=22.76(P<0.0001)						
9.8.2 2 x starting dose						
Ades 1990	10	10	-15 (4.74)		0.36%	-15[-24.29,-5.71]
Ameling 1991	331	0	-14.6 (1)		8.11%	-14.6[-16.56,-12.64]
Asmar 1991	14	0	-16 (2.45)		1.35%	-16[-20.8,-11.2]
Bateman 1979	15	0	-28.6 (2.96)		0.93%	-28.6[-34.4,-22.8]
Cilliers 1979	50	0	-12.4 (1.62)		3.09%	-12.45[-15.63,-9.27]
Davidov 1994	60	30	-8 (2.4)		1.41%	-8[-12.7,-3.3]
Giles 2014	552	277	-8 (0.8)		12.67%	-8[-9.57,-6.43]
Gostick 1977	84	0	-15.6 (1.35)		4.45%	-15.6[-18.25,-12.95]
Hansson 1975	21	23	-15.7 (3.33)		0.73%	-15.7[-22.23,-9.17]
Jeffers 1977	21	0	-24.8 (1.8)		2.5%	-24.8[-28.33,-21.27]
Lischner 1987	128	0	-8.3 (1.01)		7.95%	-8.3[-10.28,-6.32]
Myers 1983	12	0	-24 (3.3)		0.74%	-24[-30.47,-17.53]
Petrie 1980	23	0	-5.9 (2.39)		1.42%	-5.9[-10.58,-1.22]
Saunders 2007	47	20	-4.4 (2.2)		1.68%	-4.4[-8.71,-0.09]
Seedat 1980	24	0	-12.3 (2.2)		1.68%	-12.3[-16.61,-7.99]
Tseng 1993	25	14	-6.4 (3.22)		0.78%	-6.4[-12.71,-0.09]
Verdecchia 1983	20	0	-12.9 (2.12)		1.8%	-12.9[-17.06,-8.74]
Verdecchia 1988	12	0	-15 (3.31)		0.74%	-15[-21.49,-8.51]
Weiss 2007	166	40	-6.7 (1.5)		3.6%	-6.7[-9.64,-3.76]
Williams 1992	74	36	-10.7 (1.9)		2.25%	-10.7[-14.42,-6.98]
Subtotal (95% CI)					**58.25%**	**-11.57[-12.3,-10.84]**



Favour beta blocker — Favour placebo

Study or subgroup	Beta blockers N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=188.79, df=19(P<0.0001); I²=89.94%						
Test for overall effect: Z=31(P<0.0001)						
Total (95% CI)					**100%**	**-10.93[-11.48,-10.37]**
Heterogeneity: Tau²=0; Chi²=332.67, df=40(P<0.0001); I²=87.98%						
Test for overall effect: Z=38.37(P<0.0001)						
Test for subgroup differences: Chi²=7.08, df=1 (P=0.01), I²=85.87%						

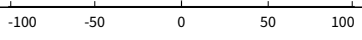
Favour beta blocker -100 -50 0 50 100 Favour placebo

Analysis 9.9. Comparison 9 Pooled overall effect, Outcome 9 Pulse pressure combined starting dose and 2 x starting dose.

Study or subgroup	Beta blockers N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
9.9.1 starting dose						
Baez 1986	12	12	-10 (4.45)		0.44%	-10[-18.72,-1.28]
Bengtsson 1976	24	0	-4 (3.34)		0.78%	-4[-10.55,2.55]
Broekman 1992	13	0	-1.2 (4.59)		0.41%	-1.2[-10.2,7.8]
Chan 1991	16	13	-9.6 (4.96)		0.35%	-9.6[-19.32,0.12]
Chan 1992	18	14	-4.8 (3.91)		0.57%	-4.8[-12.46,2.86]
Chrysant 1992	42	43	1 (2.45)		1.45%	1[-3.8,5.8]
Davidov 1994	59	30	-0.6 (2.67)		1.22%	-0.6[-5.83,4.63]
Deary 2001	34	0	-8 (2.42)		1.48%	-8[-12.74,-3.26]
Deary 2002	30	0	-8.3 (2.29)		1.66%	-8.3[-12.79,-3.81]
Dhakam 2008	16	0	-6 (3)		0.97%	-6[-11.88,-0.12]
Dhakam 2008	16	0	-3 (2.65)		1.24%	-3[-8.19,2.19]
Frishman 1995	151	75	-0.5 (1.64)		3.23%	-0.5[-3.71,2.71]
Frishman 2006	44	95	2.7 (2.61)		1.28%	2.7[-2.42,7.82]
Gostick 1977	42	0	-2.2 (1.92)		2.36%	-2.2[-5.96,1.56]
Himmelmann 1996	15	0	-3 (3.1)		0.9%	-3[-9.08,3.08]
Jeffers 1977	11	0	-2.8 (3.6)		0.67%	-2.8[-9.86,4.26]
Lacourciere 1994	19	14	-5.6 (4.26)		0.48%	-5.6[-13.95,2.75]
Maclean 1990	37	32	-3 (3.06)		0.93%	-3[-9,3]
NEB-305	244	38	-0.7 (2.05)		2.07%	-0.7[-4.72,3.32]
Papademetriou 2006	95	76	-1 (1.83)		2.59%	-1[-4.59,2.59]
Saunders 2007	41	21	-0.8 (4.07)		0.52%	-0.8[-8.78,7.18]
Stornello 1991	12	0	-2.8 (3.68)		0.64%	-2.8[-10.01,4.41]
Stumpe 1985	47	44	-7 (2.66)		1.23%	-7[-12.21,-1.79]
Tonkin 1990	15	0	1 (3.22)		0.84%	1[-5.31,7.31]
Van Bortel 1993	114	0	-6 (1.73)		2.9%	-6[-9.39,-2.61]
Van Merode 1989	29	0	0 (2)		2.17%	0[-3.92,3.92]
Van Nueten 1997	86	42	-0.5 (2.28)		1.67%	-0.5[-4.97,3.97]
Van Nueten 1998	110	59	-3 (1.96)		2.26%	-3[-6.84,0.84]
Van Nueten 1998	119	60	-3 (1.95)		2.29%	-3[-6.82,0.82]
Vanhees 1991	14	0	5.3 (3.33)		0.78%	5.3[-1.23,11.83]
Weiss 2007	165	41	2.8 (1.5)		3.86%	2.8[-0.14,5.74]
Williams 1992	74	36	-1.7 (2.59)		1.3%	-1.7[-6.78,3.38]
Subtotal (95% CI)					**45.53%**	**-2.09[-2.94,-1.23]**

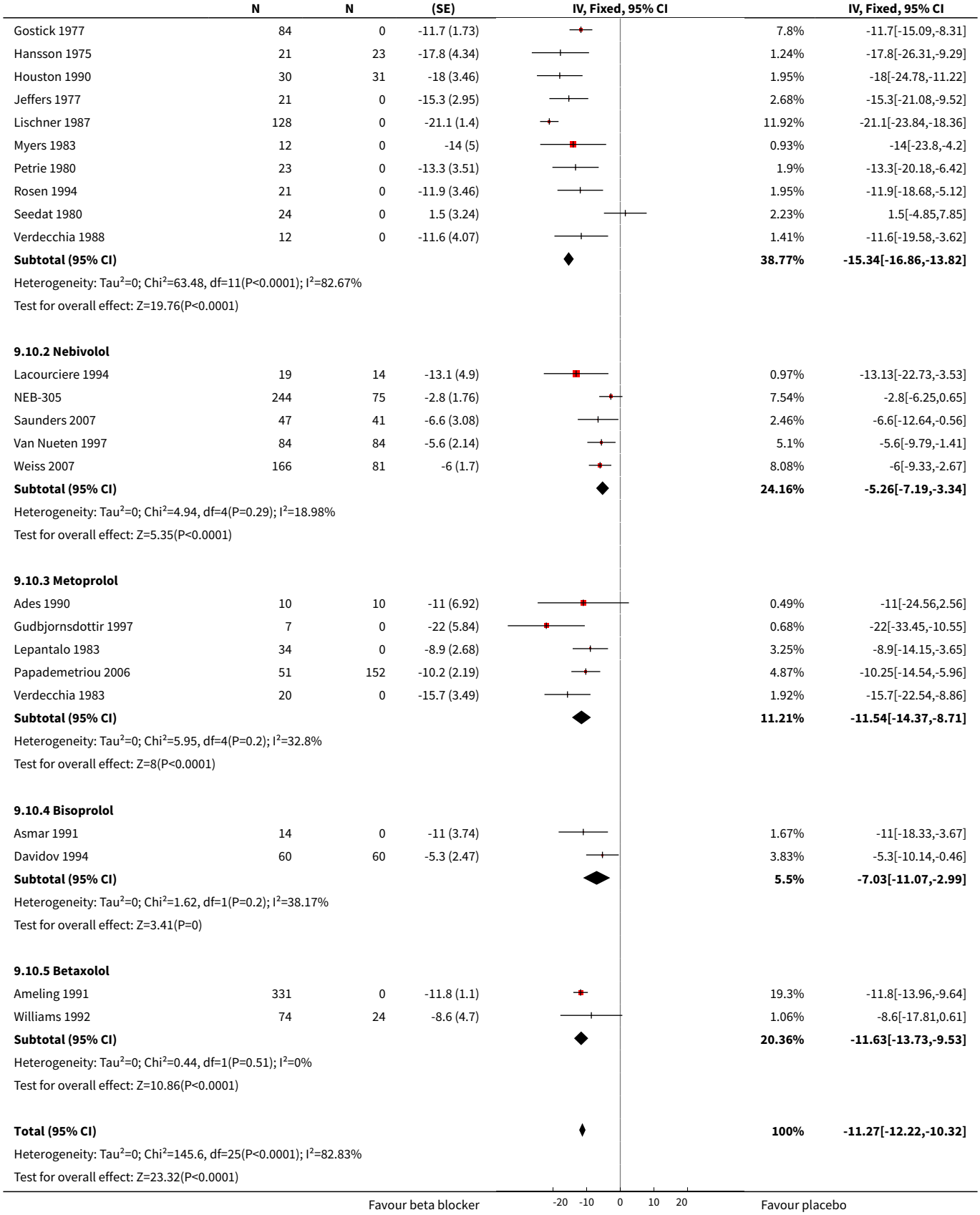
Favour beta blocker -100 -50 0 50 100 Favour placebo

Study or subgroup	Beta blockers N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=56.51, df=31(P=0); I²=45.15%						
Test for overall effect: Z=4.78(P<0.0001)						
9.9.2 2 x starting dose						
Ades 1990	10	10	-5 (6.04)		0.24%	-5[-16.84,6.84]
Ameling 1991	331	0	-3.6 (0.98)		9.05%	-3.6[-5.52,-1.68]
Asmar 1991	14	0	1 (3.49)		0.71%	1[-5.84,7.84]
Bateman 1979	15	0	-8.3 (3.42)		0.74%	-8.3[-15,-1.6]
Cilliers 1979	50	0	-1.1 (2.38)		1.53%	-1.1[-5.76,3.56]
Davidov 1994	60	30	1.9 (2.66)		1.23%	1.9[-3.31,7.11]
Giles 2014	552	277	-1 (0.96)		9.43%	-1[-2.88,0.88]
Gostick 1977	42	0	-2.8 (1.92)		2.36%	-2.8[-6.56,0.96]
Gudbjornsdottir 1997	7	0	-9 (5.23)		0.32%	-9[-19.25,1.25]
Hansson 1975	21	23	-6.5 (3.86)		0.58%	-6.5[-14.07,1.07]
Houston 1990	30	31	-10 (3)		0.97%	-10[-15.88,-4.12]
Jeffers 1977	10	0	-0.8 (3.77)		0.61%	-0.8[-8.19,6.59]
Lacourciere 1994	19	14	-3.8 (4.26)		0.48%	-3.8[-12.15,4.55]
Lepantalo 1983	34	0	0.2 (2.07)		2.03%	0.2[-3.86,4.26]
Lischner 1987	128	0	-1.7 (1.1)		7.18%	-1.7[-3.86,0.46]
Myers 1983	12	0	4 (4.63)		0.41%	4[-5.07,13.07]
NEB-305	244	37	1.2 (2.14)		1.9%	1.2[-2.99,5.39]
Papademetriou 2006	51	76	-2 (2.14)		1.9%	-2[-6.19,2.19]
Petrie 1980	23	0	-4.1 (2.6)		1.29%	-4.1[-9.2,1]
Rosen 1994	21	0	0.8 (2.72)		1.17%	0.8[-4.53,6.13]
Saunders 2007	47	20	-1.1 (3.64)		0.66%	-1.1[-8.23,6.03]
Seedat 1980	24	0	5.7 (2.54)		1.35%	5.7[0.72,10.68]
Van Nueten 1997	84	42	1.4 (2.28)		1.67%	1.4[-3.07,5.87]
Verdecchia 1983	20	0	1.6 (3.22)		0.84%	1.6[-4.71,7.91]
Verdecchia 1988	12	0	-1.8 (3.57)		0.68%	-1.8[-8.8,5.2]
Weiss 2007	166	40	0.2 (1.5)		3.86%	0.2[-2.74,3.14]
Williams 1992	74	36	-1.7 (2.59)		1.3%	-1.7[-6.78,3.38]
Subtotal (95% CI)					**54.47%**	**-1.49[-2.27,-0.71]**
Heterogeneity: Tau²=0; Chi²=41.24, df=26(P=0.03); I²=36.96%						
Test for overall effect: Z=3.74(P=0)						
Total (95% CI)					**100%**	**-1.76[-2.34,-1.19]**
Heterogeneity: Tau²=0; Chi²=98.77, df=58(P=0); I²=41.28%						
Test for overall effect: Z=5.98(P<0.0001)						
Test for subgroup differences: Chi²=1.01, df=1 (P=0.31), I²=1.47%						



Analysis 9.10. Comparison 9 Pooled overall effect, Outcome 10 SBP test for 2 x starting dose subgroup difference.

Study or subgroup	Beta blockers N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
9.10.1 Atenolol						
Bateman 1979	15	0	-27.5 (3.88)		1.55%	-27.5[-35.1,-19.9]
Cilliers 1979	50	0	-11.4 (2.7)		3.2%	-11.4[-16.69,-6.11]



Study or subgroup	Beta blockers N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Gostick 1977	84	0	-11.7 (1.73)		7.8%	-11.7[-15.09,-8.31]
Hansson 1975	21	23	-17.8 (4.34)		1.24%	-17.8[-26.31,-9.29]
Houston 1990	30	31	-18 (3.46)		1.95%	-18[-24.78,-11.22]
Jeffers 1977	21	0	-15.3 (2.95)		2.68%	-15.3[-21.08,-9.52]
Lischner 1987	128	0	-21.1 (1.4)		11.92%	-21.1[-23.84,-18.36]
Myers 1983	12	0	-14 (5)		0.93%	-14[-23.8,-4.2]
Petrie 1980	23	0	-13.3 (3.51)		1.9%	-13.3[-20.18,-6.42]
Rosen 1994	21	0	-11.9 (3.46)		1.95%	-11.9[-18.68,-5.12]
Seedat 1980	24	0	1.5 (3.24)		2.23%	1.5[-4.85,7.85]
Verdecchia 1988	12	0	-11.6 (4.07)		1.41%	-11.6[-19.58,-3.62]
Subtotal (95% CI)					**38.77%**	**-15.34[-16.86,-13.82]**
Heterogeneity: Tau²=0; Chi²=63.48, df=11(P<0.0001); I²=82.67%						
Test for overall effect: Z=19.76(P<0.0001)						
9.10.2 Nebivolol						
Lacourciere 1994	19	14	-13.1 (4.9)		0.97%	-13.13[-22.73,-3.53]
NEB-305	244	75	-2.8 (1.76)		7.54%	-2.8[-6.25,0.65]
Saunders 2007	47	41	-6.6 (3.08)		2.46%	-6.6[-12.64,-0.56]
Van Nueten 1997	84	84	-5.6 (2.14)		5.1%	-5.6[-9.79,-1.41]
Weiss 2007	166	81	-6 (1.7)		8.08%	-6[-9.33,-2.67]
Subtotal (95% CI)					**24.16%**	**-5.26[-7.19,-3.34]**
Heterogeneity: Tau²=0; Chi²=4.94, df=4(P=0.29); I²=18.98%						
Test for overall effect: Z=5.35(P<0.0001)						
9.10.3 Metoprolol						
Ades 1990	10	10	-11 (6.92)		0.49%	-11[-24.56,2.56]
Gudbjornsdottir 1997	7	0	-22 (5.84)		0.68%	-22[-33.45,-10.55]
Lepantalo 1983	34	0	-8.9 (2.68)		3.25%	-8.9[-14.15,-3.65]
Papademetriou 2006	51	152	-10.2 (2.19)		4.87%	-10.25[-14.54,-5.96]
Verdecchia 1983	20	0	-15.7 (3.49)		1.92%	-15.7[-22.54,-8.86]
Subtotal (95% CI)					**11.21%**	**-11.54[-14.37,-8.71]**
Heterogeneity: Tau²=0; Chi²=5.95, df=4(P=0.2); I²=32.8%						
Test for overall effect: Z=8(P<0.0001)						
9.10.4 Bisoprolol						
Asmar 1991	14	0	-11 (3.74)		1.67%	-11[-18.33,-3.67]
Davidov 1994	60	60	-5.3 (2.47)		3.83%	-5.3[-10.14,-0.46]
Subtotal (95% CI)					**5.5%**	**-7.03[-11.07,-2.99]**
Heterogeneity: Tau²=0; Chi²=1.62, df=1(P=0.2); I²=38.17%						
Test for overall effect: Z=3.41(P=0)						
9.10.5 Betaxolol						
Ameling 1991	331	0	-11.8 (1.1)		19.3%	-11.8[-13.96,-9.64]
Williams 1992	74	24	-8.6 (4.7)		1.06%	-8.6[-17.81,0.61]
Subtotal (95% CI)					**20.36%**	**-11.63[-13.73,-9.53]**
Heterogeneity: Tau²=0; Chi²=0.44, df=1(P=0.51); I²=0%						
Test for overall effect: Z=10.86(P<0.0001)						
Total (95% CI)					**100%**	**-11.27[-12.22,-10.32]**
Heterogeneity: Tau²=0; Chi²=145.6, df=25(P<0.0001); I²=82.83%						
Test for overall effect: Z=23.32(P<0.0001)						

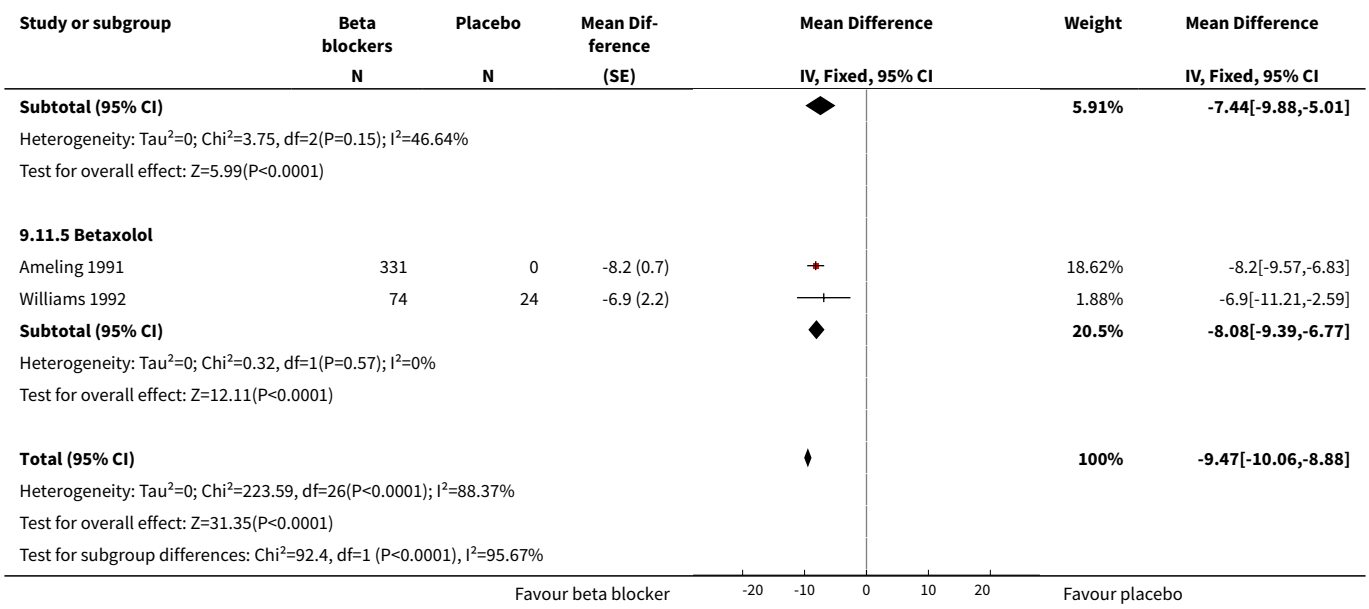
Study or subgroup	Beta blockers N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Test for subgroup differences: Chi²=69.18, df=1 (P<0.0001), I²=94.22%						

Favour beta blocker -20 -10 0 10 20 Favour placebo

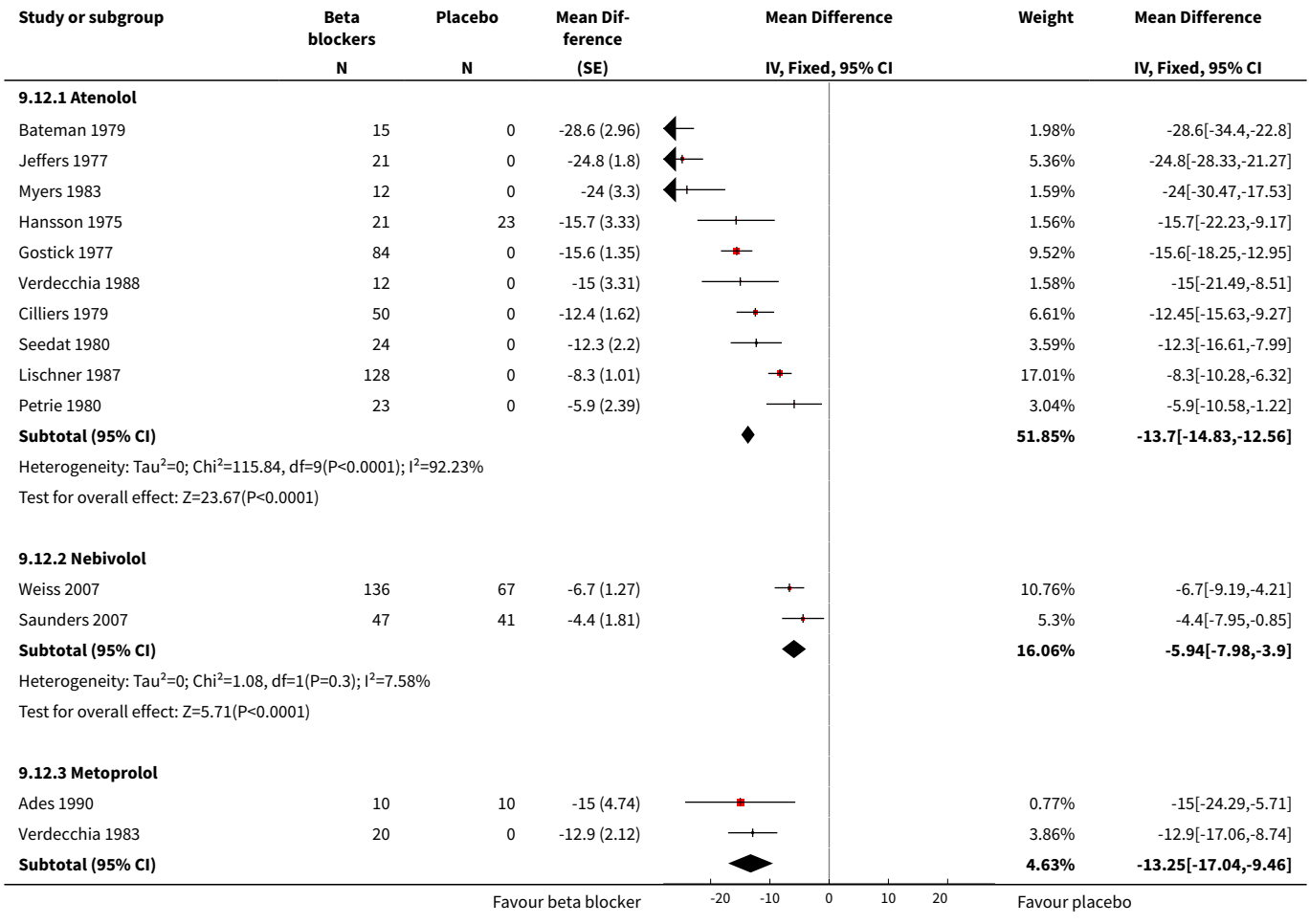
Analysis 9.11. Comparison 9 Pooled overall effect, Outcome 11 DBP test for 2 x starting dose subgroup difference.

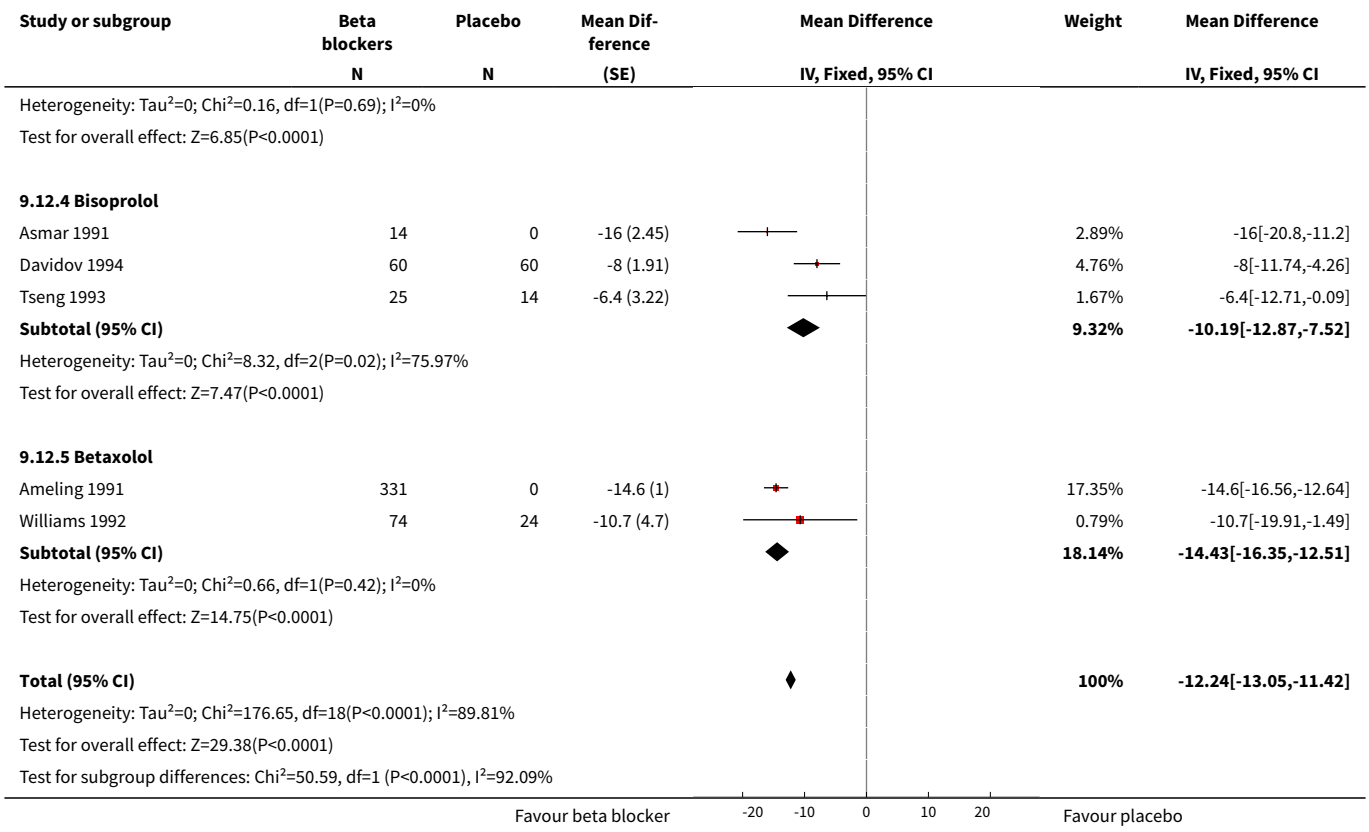
Study or subgroup	Beta blockers N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
9.11.1 Atenolol						
Bateman 1979	15	0	-19.2 (2.57)		1.38%	-19.2[-24.24,-14.16]
Cilliers 1979	50	0	-10.3 (1.78)		2.88%	-10.3[-13.79,-6.81]
Gostick 1977	84	0	-8.9 (1.14)		7.02%	-8.9[-11.13,-6.67]
Hansson 1975	21	23	-11.3 (3.04)		0.99%	-11.3[-17.26,-5.34]
Houston 1990	30	31	-8 (1.67)		3.27%	-8[-11.27,-4.73]
Jeffers 1977	21	0	-14.5 (1.95)		2.4%	-14.5[-18.32,-10.68]
Lischner 1987	128	0	-19.4 (0.92)		10.78%	-19.4[-21.2,-17.6]
Myers 1983	12	0	-18 (3)		1.01%	-18[-23.88,-12.12]
Petrie 1980	23	0	-9.2 (2.43)		1.54%	-9.2[-13.96,-4.44]
Rosen 1994	21	0	-8.9 (2.28)		1.75%	-8.88[-13.35,-4.41]
Seedat 1980	24	0	-4.2 (2.14)		1.99%	-4.2[-8.39,-0.01]
Verdecchia 1988	12	0	-9.8 (2.6)		1.35%	-9.8[-14.9,-4.7]
Subtotal (95% CI)					**36.37%**	**-12.91[-13.89,-11.93]**
Heterogeneity: Tau²=0; Chi²=106.2, df=11(P<0.0001); I²=89.64%						
Test for overall effect: Z=25.77(P<0.0001)						
9.11.2 Nebivolol						
Lacourciere 1994	19	14	-9.4 (2.84)		1.13%	-9.38[-14.95,-3.81]
NEB-305	244	75	-4 (1.08)		7.82%	-4[-6.12,-1.88]
Saunders 2007	47	41	-5.9 (1.82)		2.75%	-5.9[-9.47,-2.33]
Van Nueten 1997	84	84	-7 (1.25)		5.84%	-7[-9.45,-4.55]
Weiss 2007	166	81	-6.2 (1.06)		8.12%	-6.2[-8.28,-4.12]
Subtotal (95% CI)					**25.66%**	**-5.82[-6.99,-4.65]**
Heterogeneity: Tau²=0; Chi²=5.43, df=4(P=0.25); I²=26.37%						
Test for overall effect: Z=9.76(P<0.0001)						
9.11.3 Metoprolol						
Ades 1990	10	10	-6 (4.21)		0.51%	-6[-14.25,2.25]
Gudbjornsdottir 1997	7	0	-13 (4)		0.57%	-13[-20.84,-5.16]
Lepantalo 1983	34	0	-9.1 (1.62)		3.48%	-9.1[-12.28,-5.92]
Papademetriou 2006	51	152	-8.2 (1.36)		4.93%	-8.22[-10.89,-5.55]
Verdecchia 1983	20	0	-17.3 (2.1)		2.07%	-17.3[-21.42,-13.18]
Subtotal (95% CI)					**11.56%**	**-10.25[-11.99,-8.51]**
Heterogeneity: Tau²=0; Chi²=15.49, df=4(P=0); I²=74.18%						
Test for overall effect: Z=11.53(P<0.0001)						
9.11.4 Bisoprolol						
Asmar 1991	14	0	-12 (2.98)		1.03%	-12[-17.84,-6.16]
Davidov 1994	60	60	-7.2 (1.56)		3.75%	-7.2[-10.26,-4.14]
Tseng 1993	25	14	-4.1 (2.84)		1.13%	-4.1[-9.67,1.47]

Favour beta blocker -20 -10 0 10 20 Favour placebo



Analysis 9.12. Comparison 9 Pooled overall effect, Outcome 12 Heart rate test for 2 x starting dose subgroup difference.





APPENDICES

Appendix 1. Search strategies

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update
Search Date: 15 October 2015

---

1 exp adrenergic beta-antagonists/ (79534)

2 (beta adj2 (adrenergic? or antagonist? or block$ or receptor?)).tw. (90056)

3 acebutolol.mp. (1071)

4 exp alprenolol/ (2182)

5 alprenolol.mp. (1560)

6 amosulalol.mp. (45)

7 arotinolol.mp. (83)

8 atenolol.mp. (7428)

9 befunolol.mp. (113)

10 betaxolol.mp. (944)

11 bevantolol.mp. (81)

12 exp bisoprolol/ (889)

13 bisoprolol.mp. (1271)

14 bopindolol.mp. (136)

15 bucindolol.mp. (173)

16 bucumolol.mp. (6)

17 bufetolol.mp. (12)

18 bufuralol.mp. (396)

19 bunitrolol.mp. (101)

20 exp bupranolol/ (196)

21 bupranolol.mp. (328)

22 butofilolol.mp. (10)

23 carazolol.mp. (145)

24 exp carteolol/ (319)

25 carteolol.mp. (428)

26 carvedilol.mp. (2755)

27 exp celiprolol/ (388)

28 celiprolol.mp. (492)

29 cetamolol.mp. (15)

30 cloranolol.mp. (2)

31 cyanopindolol.mp. (635)

32 deacetylmetipranolol.mp. (5)

33 dihydroalprenolol.mp. (1687)

34 dilevalol.mp. (131)

35 epanolol.mp. (58)

36 esmolol.mp. (1098)

37 indenolol.mp. (50)

38 iodocyanopindolol.mp. (1048)

39 exp labetalol/ (1748)

40 labetalol.mp. (2229)

41 landiolol.mp. (236)

42 exp levobunolol/ (228)

43 levobunolol.mp. (277)

44 mepindolol.mp. (86)

45 exp metoprolol/ (5024)

46 metoprolol.mp. (6976)

47 exp metipranolol/ (262)

48 metipranolol.mp. (315)

49 moprolol.mp. (17)

50 exp nadolol/ (783)

51 nadolol.mp. (1207)

52 nadoxolol.mp. (8)

53 nebivolol.mp. (761)

54 nifenalol.mp. (13)

55 nipradilol.mp. (162)

56 oxprenolol.mp. (1340)

57 exp penbutolol/ (176)

58 penbutolol.mp. (259)

59 exp pindolol/ (3715)

60 pindolol.mp. (4618)

61 exp practolol/ (1546)

62 practolol.mp. (2157)

63 pronethalol.mp. (211)

64 exp propranolol/ (31625)

65 propranolol.mp. (42477)

66 proxodolol.mp. (23)

67 exp sotalol/ (1975)

68 sotalol.mp. (2930)

69 sulfinalol.mp. (5)

70 talinolol.mp. (240)

71 tertatolol.mp. (175)

72 tilisolol.mp. (28)

73 exp timolol/ (3463)

74 timolol.mp. (4378)

75 toliprolol.mp. (16)

76 xibenolol.mp. (4)

77 or/1-76 (145421)

78 hypertension/ (202792)

79 hypertens$.tw. (322888)

80 exp blood pressure/ (258033)

81 (blood pressure or bloodpressure).mp. (368499)

82 or/78-81 (620920)

83 randomized controlled trial.pt. (413758)

84 controlled clinical trial.pt. (91901)

85 randomized.ab. (305710)

86 placebo.ab. (158376)

87 clinical trials as topic/ (179345)

88 randomly.ab. (216422)

89 trial.ti. (135204)

90 or/83-89 (941528)

91 animals/ not (humans/ and animals/) (4036142)

92 90 not 91 (863690)

93 77 and 82 and 92 (8822)

94 93 and (2014$ or 2015$).ed. (236)

95 remove duplicates from 94 (213)

****

Database: Cochrane Central Register of Controlled Trials <Issue 10, 2015> via Cochrane Register of Studies Online
Search date: 15 October 2015

#1 MESH DESCRIPTOR Adrenergic beta-Antagonists EXPLODE ALL TREES 9197

#2 (acebutolol or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevanolol or bisoprolol or bopindolol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bupranolol or butofilolol or carazolol or carteolol or carvedilol or celiprolol or cetamolol or cloranolol or cyanopindolol or deacetylmetipranolol or dihydroalprenolol or dilevalol or epanolol or esmolol) 5792

#3 (indenolol or iodocyanopindolol or labetalol or levobunolol or mepindolol or metipranolol or metoprolol or nadolol or nadoxolol or nebivolol or nifenalol or nipradilol or oxprenolol or penbutolol or pindolol or practolol or pronethalol or propranolol or sotalol or sulfinalol or talinolol or tertatolol or tilisolol or timolol or toliprolol or xibenolol) 10487

#4 #1 OR #2 OR #3

#5 MESH DESCRIPTOR Hypertension 13058

#6 hypertens*:TI,AB 30044

#7 MESH DESCRIPTOR Blood Pressure EXPLODE ALL TREES 22928

#8 blood pressure*:TI,AB 39350

#9 #5 OR #6 OR #7 OR #862225

#10 #4 AND #9 7961

****

Database: Embase <1980 to 2015 October 14>
Search Date: 15 October 2015
---
1 exp beta adrenergic receptor blocking agent/ (233618)

2 (beta adj2 (adrenergic? or antagonist? or block$ or receptor?)).tw. (101743)

3 acebutolol.mp. (4473)

4 exp alprenolol/ (3668)

5 alprenolol.mp. (3863)

6 amosulalol.mp. (122)

7 arotinolol.mp. (239)

8 atenolol.mp. (28052)

9 befunolol.mp. (306)

10 betaxolol.mp. (3108)

11 bevantolol.mp. (221)

12 exp bisoprolol/ (6963)

13 bisoprolol.mp. (7444)

14 bopindolol.mp. (293)

15 bucindolol.mp. (995)

16 bucumolol.mp. (26)

17 bufetolol.mp. (39)

18 bufuralol.mp. (776)

19 bunitrolol.mp. (271)

20 exp bupranolol/ (747)

21 bupranolol.mp. (777)

22 butofilolol.mp. (33)

23 carazolol.mp. (474)

24 exp carteolol/ (1392)

25 carteolol.mp. (1416)

26 carvedilol.mp. (11838)

27 exp celiprolol/ (1435)

28 celiprolol.mp. (1462)

29 cetamolol.mp. (41)

30 cloranolol.mp. (45)

31 cyanopindolol.mp. (1506)

32 deacetylmetipranolol.mp. (28)

33 dihydroalprenolol.mp. (2794)

34 dilevalol.mp. (373)

35 epanolol.mp. (104)

36 esmolol.mp. (4190)

37 indenolol.mp. (135)

38 iodocyanopindolol.mp. (675)

39 exp labetalol/ (8871)

40 labetalol.mp. (9028)

41 landiolol.mp. (403)

42 exp levobunolol/ (909)

43 levobunolol.mp. (919)

44 mepindolol.mp. (346)

45 exp metoprolol/ (27178)

46 metoprolol.mp. (30056)

47 exp metipranolol/ (936)

48 metipranolol.mp. (951)

49 moprolol.mp. (50)

50 exp nadolol/ (4932)

51 nadolol.mp. (5044)

52 nadoxolol.mp. (27)

53 nebivolol.mp. (2959)

54 nifenalol.mp. (95)

55 nipradilol.mp. (365)

56 oxprenolol.mp. (4172)

57 exp penbutolol/ (792)

58 penbutolol.mp. (817)

59 exp pindolol/ (8423)

60 pindolol.mp. (8696)

61 exp practolol/ (2859)

62 practolol.mp. (3073)

63 pronethalol.mp. (105)

64 exp propranolol/ (75390)

65 propranolol.mp. (80073)

66 proxodolol.mp. (30)

67 exp sotalol/ (10836)

68 sotalol.mp. (11108)

69 sulfinalol.mp. (16)

70 talinolol.mp. (607)

71 tertatolol.mp. (330)

72 tilisolol.mp. (150)

73 exp timolol/ (9884)

74 timolol.mp. (12468)

75 toliprolol.mp. (133)

76 xibenolol.mp. (98)

77 or/1-76 (284190)

78 exp hypertension/ (531015)

79 hypertens$.tw. (462678)

80 (blood pressure or bloodpressure).mp. (463482)

81 or/78-80 (939766)

82 randomized controlled trial/ (386041)

83 crossover procedure/ (44726)

84 double-blind procedure/ (124191)

85 (randomized or randomly).ab. (716198)

86 (crossover$ or cross-over$).tw. (76212)

87 placebo$.ab. (214767)

88 (doubl$ adj blind$).tw. (155583)

89 or/82-88 (991842)

90 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) (5388776)

91 89 not 90 (877051)

92 77 and 81 and 91 (11565)

****

Database: Hypertension Group Specialised Register
Search Date: 15 October 2015

#1 MeSH DESCRIPTOR Adrenergic beta-Antagonists EXPLODE ALL TREES (1480)

#2 ((acebutolol or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevanolol or bisoprolol or bopindolol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bupranolol or butofilolol or carazolol or carteolol or carvedilol or celiprolol or cetamolol or cloranolol or cyanopindolol or deacetylmetipranolol or dihydroalprenolol or dilevalol or epanolol or esmolol)) (2507)

#3 ((indenolol or iodocyanopindolol or labetalol or levobunolol or mepindolol or metipranolol or metoprolol or nadolol or nadoxolol or nebivolol or nifenalol or nipradilol or oxprenolol or penbutolol or pindolol or practolol or pronethalol or propranolol or sotalol or sulfinalol or talinolol or tertatolol or tilisolol or timolol or toliprolol or xibenolol)) (325)

#4 #1 OR #2 OR #3 (5951)

#5 (RCT):DE OR (Review OR Meta-Analysis):MISC2 (21968)

#6 #4 AND #5 (3725)

****

Database: ClinicalTrials.gov (via Cochrane Register of Studies)
Search Date: 15 October 2015

Study type: Interventional Studies
Conditions: hypertension
Interventions: (beta blocker) or (adrenergic beta-antagonist)
Outcome Measures: blood pressure
Search terms: randomized

****

F E E D B A C K

Comment, 17 March 2016

Summary

Thank you for an immense amount of painstaking work on this. I was also pleasantly surprised to see that access to the data was so easy. I had not realised this was possible, and will take it up with our ME to see how to do this with our own reviews.
I was surprised to see that despite over 5,000 participants in many studies for SPB, for instance, your GRADE assessment was lo, indicating a huge degree of uncertainty. After all, this indicates that: "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." So despite dozens of trials and thousands of participants, we don't know if these drugs drop BP. Does that seem likely?

To my mind it seemed unlikely. I did wonder at the small size of some of the studies (lowest 8 participants). Half the studies with a treatment size below 50 could be lost, and still retain 90% of participants. The Drop in BP is still 8.3 (7.7 to 8.9) with 4659 participants. So small size isn't an issue, or not a big one, in this case in terms of overestimating treatment effect.
But you do give a lot of weight to asymmetric funnel plots and ascribe this to possible publication bias. Now a systematic review of methods to detect publication bias (J Clin Epidemiol. 2000 Feb;53(2):207-16.) and didn't really indicate that we can rely on these tests to positively detect publication bias. And to overcome results from 5,000 participants with a mean drop in BP of over 9 mm in your analysis would require a massive amount of unpublished null or negative data - quite beyond the realms of possibility. It would be a massive scandal.
I would suggest that your use of GRADE is possibly wrong. For the most part the studies, and especially the larger ones, looked relatively unbiased, or at least without flags for high risk of bias.
The problem with GRADE is that it asks us to downgrade studies for all sorts of reasons, some of which may even have some evidence of a small effect on the estimate of efficacy, but many of which do not. Other major issues (small size being one) are ignored.
Anyway, it would be helpful to this reader to know whether or not you really think there is a chance that the possible bias is so great as to suggest that these drugs don't work.

Reply

Thank you for your comment. We agree with you that this review does prove that beta-1 selective beta blockers do lower BP.
We down GRADED the evidence to low because we think that the current overall effect estimate (-10/-8 mmHg) is likely to be exaggerated. As explained in the discussion the pooled effect of trials measuring the BP at trough was -8/-7 mmHg and in a separate analysis the pooled effect of the parallel trials, which are larger and of better quality, was -7/-6 mmHg [1]. We think that these estimates are closer to the true BP lowering effect of beta-1 selective blockers.
We recognize the limitation of the GRADE assessment tool. However, we believe that our downgrade to low is reasonable given the limitations of the tool. Both SBP and DBP analyses contain multiple outliers that exaggerate the effect estimate, and there is an inherent risk of loss of blinding in all beta-blocker trials due to the effect on heart rate. We also have reason to believe that trials in which the BP lowering effect was absent or of small magnitude are unlikely to be published leading to a high risk of publication bias. We have discussed this to a greater extent in the non-selective beta blocker review [2].
References:
1. Wong GW, Wright JM. Are the estimates of blood pressure (BP) lowering effect the same in parallel and cross-over trials [abstract]? In: the 23rd Cochrane Colloquium; 2015 Oct 3-7; Vienna, Austria. John Wiley & Sons, Ltd.; 2015. Abstract LRO 5.4.

2. Wong GWK, Wright JM. Blood pressure lowering efficacy of nonselective beta-blockers for primary hypertension. Cochrane Database of Systematic Reviews 2014, Issue 2. Art. No.: CD007452. DOI: 10.1002/14651858.CD007452.pub2.

Contributors

Name: Andrew Moore
Email Address: andrew.moore@ndcn.ox.ac.uk
Affiliation: University of Oxford, UK

WHAT'S NEW

Date	Event	Description
23 April 2016	Feedback has been incorporated	New feedback and authors' reply incorporated

HISTORY

Protocol first published: Issue 4, 2008
Review first published: Issue 3, 2016

Date	Event	Description
18 June 2010	Amended	Protocol was amended: added a second author, clarified inclusion criteria to accept cross-over studies and double-blinded studies. Updated background section. Removed acebutolol from the beta-1 selective list as it belongs to the partial agonist group.

CONTRIBUTIONS OF AUTHORS

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

Heidi Boyda aided in the identifying of the included studies, in verifying the data extraction, and reviewing the final draft of the manuscript.

James Wright formulated the idea for the review, developed the basis for the protocol and participated in the interpretation and writing of the review.

DECLARATIONS OF INTEREST

Gavin Wong: nothing to declare
Heide Boyda: nothing to declare
James 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.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are no differences between the protocol and review.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic beta-Antagonists [administration & dosage] [*therapeutic use]; Antihypertensive Agents [administration & dosage] [*therapeutic use]; Blood Pressure [drug effects]; Diastole [drug effects]; Essential Hypertension; Heart Rate [drug effects]; Hypertension [*drug therapy]; Randomized Controlled Trials as Topic; Systole [drug effects]

MeSH check words

Humans