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[Intervention Review]

Evening versus morning dosing regimen drug therapy for hypertension

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ABSTRACT

Background

Variation in blood pressure levels display circadian rhythms. The morning surge in blood pressure is known to increase the risk of myocardial events in the first several hours post awakening. A systematic review of the administration-time-related-effects of evening versus morning dosing regimen of antihypertensive drugs in the management of patients with primary hypertension has not been conducted.

Objectives

To evaluate the administration-time-related-effects of antihypertensive drugs administered as once daily monotherapy in the evening versus morning administration regimen on all cause mortality, cardiovascular morbidity and reduction of blood pressure in patients with primary hypertension.

Search methods

We searched Cochrane CENTRAL on Ovid (4th Quarter 2009), Ovid MEDLINE (1950 to October 2009), EMBASE (1974 to October 2009), the Chinese Biomedical literature database (1978 to 2009) and the reference lists of relevant articles. No language restrictions were applied.

Selection criteria

Randomized controlled trials comparing the administration-time-related effects of evening with morning dosing monotherapy regimens in patients with primary hypertension were included. Patients with known secondary hypertension, shift workers or white coat hypertension were excluded.

Data collection and analysis

Two authors independently extracted data and assessed trial quality. Disagreements were resolved by discussion or a third reviewer. Data synthesis and analysis were done using RevMan 5.1. Random effects meta-analysis and sensitivity analysis were conducted.

Main results

21 randomized controlled trials (RCTs) in 1,993 patients with primary hypertension met the inclusion criteria for this review - ACEIs (5 trials), CCBs (7 trials), ARBs (6 trials), diuretics (2 trials), alpha-blockers (1 trial), and beta-blockers (1 trial). Meta-analysis showed significant heterogeneity across trials.

No RCT reported on all cause mortality, cardiovascular mortality, cardiovascular morbidity and serious adverse events.

There was no statistically significant difference for overall adverse events (RR=0.78, 95%CI: 0.37 to 1.65) and withdrawals due to adverse events (RR=0.53, 95%CI: 0.26 to 1.07).

No significant differences were noted for morning SBP (-1.62 mm Hg, 95% CI: -4.19 to 0.95) and morning DBP (-1.21 mm Hg, 95% CI: -3.28 to 0.86); but 24-hour BP (SBP: -1.71 mm Hg, 95% CI: -2.78 to -0.65; DBP: -1.38 mm Hg, 95% CI: -2.13 to -0.62) showed a statistically significant difference.

Authors' conclusions

No RCT reported on clinically relevant outcome measures - all cause mortality, cardiovascular morbidity and morbidity. There were no significant differences in overall adverse events and withdrawals due to adverse events among the evening versus morning dosing regimens. In terms of BP lowering efficacy, for 24-hour SBP and DBP, the data suggests that better blood pressure control was achieved with bedtime dosing than morning administration of antihypertensive medication, the clinical significance of which is not known.

PLAIN LANGUAGE SUMMARY

Time effects of blood pressure lowering drugs for the treatment of high blood pressure

Elevated blood pressure is an important public health problem and once daily dosing regimen with blood pressure lowering drugs are recommended to reduce risk of strokes and heart attacks. This review examined the administration-time-related effects of once-daily evening versus morning regimen on death, cardiovascular outcomes and blood pressure reduction. The interventions included chronotherapeutic delivery formulations and conventional antihypertensive agents. 21 trials, involving 1,993 patients with primary hypertension were identified. We concluded that evening dosing with antihypertensive drugs had a slightly better blood pressure control than the morning dosing regimen in 24-hour BP, but its effect on death and adverse cardiovascular outcomes is not known.

BACKGROUND

Description of the condition

Elevated blood pressure or hypertension (defined as resting blood pressure levels of 140/90 mm Hg or more) is estimated to affect 20% of the adult population in both developed and developing countries. It is associated with an increased risk of death, and cardiovascular disease (CVD).

Six main classes of antihypertensive drugs are used worldwide: diuretics, angiotensin converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs), beta-adrenergic receptor blockers (BBs), angiotensin II receptor blockers (ARBs) and alpha-adrenergic antagonists. It is a well known fact that variation in blood pressure levels display circadian rhythms. The morning surge in blood pressure is known to increase the risk of myocardial events in the first several hours post awakening. WHO recommends using once daily long acting antihypertensive drugs, since they provide a more consistent 24-hour BP control, reduce BP variability, and improve adherence to therapy (Guidelines Subcommittee 1999). Antihypertensive drugs are traditionally administered either as monotherapy or in combinations in the morning upon arising from bed. This is mainly because this approach has been applied in the vast majority of outcome trials that showed benefits of treatment in reducing the risk of CVD. Another important reason is that a once-daily morning regimen improves patients' adherence to the long-term treatment (Chobanian 2003, Waeber 1999). However, the administration-time-effects of evening versus morning dosing regimen of antihypertensive drugs on clinically relevant outcomes such as death and cardiovascular outcomes in the management of patients with primary hypertension has not been studied in a systematic review.

Description of the intervention

In this review, the conventional or routine administration of antihypertensive drug therapy for essential hypertension means dosing in the morning upon arising from bed. The traditional antihypertensive agents include long acting medications or the conventional (so-called homeostatically formulated) drugs administered without regard to BP circadian rhythm. They differ from chronotherapeutic formulations which are specially designed to provide peak plasma concentrations during the early morning hours when BP rises to peak and provide lower concentrations at night (Smolensky 1999).

Chronotherapeutics is defined as the purposeful timing of medications, whether or not they utilize special drug release technology, to proportion serum and tissue concentrations in synchrony with known circadian rhythms in disease processes and symptoms as a means of enhancing beneficial outcomes and/or attenuating or averting adverse effects (Smolensky 1996). The chronotherapy of hypertension specifically entails significant attenuation of the accelerated morning rise of SBP and DBP and this may be achieved through the use of special drug-delivery technology (Smolensky 2005) or by changing the dosing timing of conventional BP-lowering medications (Hermida 2004a, Hermida 2005e).

Ambulatory blood pressure monitoring (ABPM) is a valuable technique to determine antihypertensive efficacy both in clinical practice and in research settings (O'Brien 1991). The use of such monitoring makes it feasible to follow the time course of BP variation around the clock in large groups of subjects. Compared with traditional resting BP measurement, it allows the assessment of duration of action of antihypertensive agents and compensates for most of the limitations of office determinations (Hermida 1999). It also makes it possible to exclude pharmacotherapy in patients who have white coat hypertension, and allows the evaluation of the consistency of the antihypertensive effect of new drug-chronotherapeutic agents (Canter 1994).

How the intervention might work

Blood pressure (BP) varies throughout the day, has a distinct and reproducible 24-hour circadian rhythm in both normotensive and uncomplicated hypertensive patients (Hermida 2002, O'Brien 2003, White 1997a, White 1999). In patients who are awake during the daytime and asleep during the nighttime, their BP and HR have showed a typical circadian variation, with lower BP levels during nighttime sleep and an abrupt rise upon arising in the morning (Pickering 1993, White 1989, White 1997a, White 1999). This pattern is rapidly reversed when individuals work night shifts and sleep during the day (Sunderg 1988). It was previously reported that the morning BP surge upon arising from bed appeared to parallel the morning surge in the incidence of cardiovascular events and was significantly associated with a greater target organ damage and higher cardiovascular events risk (Kario 2003, Kuwajima 1995, Muller 1989, White 2001). Based on this rationale, it is hypothesized that antihypertensive medication targeted for early morning BP control in addition to providing 24-hour BP control would result in a significant reduction of cardiovascular events in hypertensive patients. In other words, the medication is considered to lower BP consistently as well as reduce excessive peaks in pressure that may pose an additional cardiovascular risk.

Why it is important to do this review

Based on the above mentioned relationship, researchers began to apply the science of chronotherapeutics, or timing of drug effect to the treatment of essential hypertension to improve cardiovascular outcomes. A number of studies investigated the administration-time-dependent antihypertensive efficacy, e.g. ACEIs such as ramipril (Hermida 2009a, Myburgh 1995), trandolapril (Kuroda 2004), perindopril (Morgan 1997), and quinapril (Palatini 1992); CCBs such as diltiazem (Glasser 2003), nifedipine (Hermida 2007, Hermida 2008, Hermida 2009b), cilnidipine (Kitahara 2004), nisoldipine (White 1999a) and amlodipine (Nold 1998, Qiu 2003); diuretics such as torasemide (Calvo 2006a, Hermida 2008a); ARBs such as valsartan (Hermida 2003, Hermida 2005a, Hermida 2005b), telmisartan (Hermida 2007a), and olmesartan (Hermida 2009); α-blockers such as doxazosin (Hermida 2004). A few clinical trials had found that nighttime dosing was more effective than morning administration to optimize morning BP control while maintaining 24-hour efficacy (Glasser 2003, White 2004), but another trial found no difference in morning SBP between the two groups (Wright 2004). One large trial compared verapamil versus atenolol or HCTZ on reduction of BP and cardiovascular risk (Black 2003).

A study in hypertensive rats showed that dosing an ACE inhibitor, trandolapril, at night, had a better organ protective effect than dosing in the morning (Sugimoto 2001). Clinical trials have been performed in hypertensive patients by changing the time of dosing from morning to evening to enhance their effectiveness on cardiovascular outcomes (Fujimura 1999). There are also a few non-

systematic or traditional reviews focusing on this issue (Ezeugo 2009, Hermida 2007C, Hermida 2007d, Ohmori 2005, Stergiou 2007), some of which reported that nighttime administration of antihypertensive drugs had a larger blood pressure lowering effect during nighttime and the early morning hours. There is considerable evidence that the morning administration gives its full effect during daytime activities and a lesser effect during nighttime and the early morning hours, whereas bedtime administration has a larger effect during nighttime and the early morning hours. However, no systematic review and meta-analysis has been conducted to confirm these findings. It might be argued that bedtime administration should be considered as an alternative strategy that has the potential benefits to provide more effective cardiovascular protection.

OBJECTIVES

To evaluate the effectiveness of administration-time-related effects of once-daily evening versus conventional morning dosing antihypertensive drug therapy regimen on all cause mortality, cardiovascular mortality and morbidity, total adverse events, withdrawals due to adverse effects and reduction of systolic and diastolic blood pressure in patients with primary hypertension.

The secondary objective is to also compare once daily administration of antihypertensive chronotherapeutic delivery system (evening administration) versus a conventional monotherapy regimen (morning administration) in the management of patients with essential hypertension.

METHODS

Criteria for considering studies for this review

Types of studies

Included studies must be randomised controlled trials of at least 3 weeks treatment duration. Randomized cross-over trials which were restricted to designs with 2 interventions and 2 treatment periods were also included.

Types of participants

Adult patients with primary (essential) hypertension whose systolic and/or diastolic blood pressure levels were 140/90 mm Hg or greater were included. Patients with secondary causes of hypertension, white coat hypertension and alternating shift workers were excluded.

Types of interventions

- Intervention: Monotherapy with an antihypertensive drug + administered once-daily in the evening *
- Control: Monotherapy with the same antihypertensive drug at the same dose administered once-daily in the morning **.

+ Antihypertensive drug belonging to any one of the following six classes: angiotensin converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs), beta-blockers (BBs), diuretics, angiotensin II receptor blockers (ARBs) and alpha-blockers

*Evening administration was defined from 6:00 p.m. to 12:00 midnight

**Morning administration was defined from 6:00 a.m. to 12:00 noon

For the comparison between chronotherapeutic and conventional monotherapy drug regimen, the chronotherapeutic group should take the same drug and dose (evening administration) as the conventional regimen (morning administration only).

Types of outcome measures

Primary outcomes Death from all causesCardiovascular mortalityCardiovascular morbidity (stroke, myocardial infarction, congestive heart failure, aortic aneurysm)

Primary outcomes

- Death from all causes
- Cardiovascular mortality
- Cardiovascular morbidity (stroke, myocardial infarction, congestive heart failure, aortic aneurysm)

Secondary outcomes

- Serious adverse events
- Overall adverse effects
- Withdrawals from treatment due to adverse effects
- Change from baseline in 24-hour mean SBP and DBP by ambulatory BP monitoring
- Change from baseline in morning SBP and DBP (assessed by ambulatory BP monitoring during the periods from 6 a.m. to 12 noon)

Search methods for identification of studies

Electronic searches

We searched the following electronic databases for randomised controlled trials (RCTs):

1. The Cochrane Central Register of Controlled Trials (CENTRAL) on Ovid (4th Quarter 2009)
2. Ovid MEDLINE from 1950 to October 2009
3. EMBASE.com from 1974 to October 2009
4. Chinese Biomedical Literature Database (CBLD) from 1978 to 2009

The Electronic databases were searched using a strategy combining a variation of 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 relating to chronotherapy and hypertension. There were no language restrictions. The MEDLINE search strategy was translated into the other databases using the appropriate controlled vocabulary as applicable. The full electronic database search strategies are in Appendix 1, Appendix 2, Appendix 3, Appendix 4.

Searching other resources

1. Reference lists of meta-analyses and relevant reviews were identified. Bibliographic citations from retrieved studies were also hand-searched.
2. Authors of trials reporting incomplete information were contacted to provide the missing information.

Data collection and analysis

Selection of studies

All titles and the abstracts resulting from the search strategies were screened independently by two reviewers (Xu Ping and Zhao Ping). Articles were rejected on initial screening if they clearly did not meet the pre-specified inclusion criteria. The full text of the remaining articles were then retrieved and translated to English where required. The bibliographies of pertinent articles, reviews and texts were searched for additional citations. Studies which met the inclusion criteria were examined in detail. Reasons for excluding any study were documented. Trials with more than one publication were counted only once. Discrepancies between reviewers were resolved by discussion, and when necessary by a third reviewer (Wan Chaomin or Wang Zhengrong). For the crossover trials, carryover effects were also assessed.

Data extraction and management

Data was extracted independently by two reviewers Xu Ping and Zhao Ping using a standard form and then cross-checked. The differences in interpretation of data were resolved through further examination and consensus between the reviewers. If data were presented in tables, text or in figures, the numeric data were preferred because of possible measurement error when estimating from graphs. The data extracted from each study included patient characteristics, methods, interventions, outcomes and notes as mentioned in the table of included studies. All data, regardless of compliance or completion of follow up, was collected in order to allow for an intention to treat analysis.

In the case of missing information in the included studies, investigators were contacted by email to obtain the missing information. In the case of missing values for standard deviation of the change in blood pressure, the standard deviation was imputed based on the information in the same trial or from other trials using the same class of drug. The following hierarchy (listed from high to low preference) was used to impute standard deviation values:

1. Pooled standard deviation calculated either from the statistic corresponding to an exact p-value reported or from the 95% confidence interval of the mean difference between two groups.
2. Standard deviation of blood pressure at the end of treatment.
3. Standard deviation of blood pressure at baseline (except if this measure was used for entry criteria). (Musini 2009)
4. Weighted mean standard deviation of change in blood pressure from other trials.

Assessment of risk of bias in included studies

Two independent reviewers (Xu Ping and Zhao Ping) assessed the risk of bias of all included trials and completed a Risk of Bias Table as described in chapter 8 of the Cochrane Handbook.

Measures of treatment effect

For evaluation of the primary outcomes (mortality, cardiovascular mortality, cardiovascular morbidity and adverse events), data on the total number of patients with at least one event within each trial was to be extracted and comparisons between groups would be presented as relative risk ratios with corresponding 95% confidence intervals. However, this was not done as none of the included trials reported any of these outcome measures.

Nine crossover RCTs that were included provided data on SBP and DBP. The data were obtained from texts, figures and tables. These data were entered using generic inverse variance. Subsequently for all other parallel group RCTs' blood pressure data were entered in a similar manner.

For parallel trials, we assessed the tolerability of the intervention by calculating the risk ratio (RR) of adverse events in the evening administration as compared to morning administration treatment arms. Random effects model was used to calculate a pooled risk ratio. Crossover trials are designed with the intention that all participants receive both the active and control interventions, and the treatment effect is estimated from the differences in response of the same participant to the different treatments. Hence participants who withdraw from either treatment cannot be included in the analysis and so the question of differential withdrawal between treatment arms does not arise.

Dealing with missing data

In general if there were missing data, the authors of the study were contacted using e-mail for clarification. In cases where missing information was ultimately not available, the best estimate was included based on information in the same trial or information from other trials using the same class of drug. For instance, if standard error of the change for blood pressure was not provided, the value was imputed using the pooled standard error of change data from other similar trials and by calculating a weighted pooled standard error.

Assessment of heterogeneity

Heterogeneity between trial results was tested using the I^2 statistic where percentages greater than 50% were taken to indicate significant heterogeneity. If heterogeneity was detected for outcomes, a random effects model was used.

Assessment of reporting biases

In the event that missing data was imputed, sensitivity analysis was performed to see if results were sensitive to the assumptions being made. The potential impact of missing data has been reviewed in the discussion section.

Data synthesis

Cochrane Review Manager software, RevMan 5.1, was used for all data syntheses and analyses.

Quantitative analyses of outcomes were based on intention-to-treat principles as much as possible. Relative risks were calculated for dichotomous clinical outcomes but was not done as none of the trials provided this data. Data for blood pressure reduction was combined using generic inverse variance, which entailed entering the end of study mean blood pressure difference and pooled standard error of the difference.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were performed, grouping the trials into those using drugs from different antihypertensive classes: α-blockers, β-blockers, ACEIs, ARBs, CCBs, and diuretics.

Sensitivity analysis

We intended to conduct a sensitivity analysis by methodological quality:

1. Exclusion of non double-blind trials.
2. Exclusion of trials not reporting the method of generation of the allocation sequence.
3. Exclusion of trials not reporting the method of blinding.
4. Exclusion of trials with inadequate allocation concealment.
5. Exclusion of trials with imputed data.

The planned sensitivity analysis could not be conducted as few trials met the inclusion criteria and data within those trials was limited.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Results of the search

The search strategy found 8416 references in CENTRAL, MEDLINE, EMBASE and CBLD, whose titles and abstracts were screened by Zhao P and Xu P. 8318 references were excluded and the remaining 98 articles were retrieved for detailed evaluation. On detailed examination, we excluded 68 articles (64 trials) for the following reasons: not a RCT (16 trials), treatment period less than three weeks (7 trials), placebo controlled with no comparator treatment arm (4 trials), triple-way crossover RCT (2 trials), not monotherapy (13 trials), healthy people (2 trials), no relevant endpoints (11 trials), lack of data (1 trial), different drugs in comparator arms (6 trials), different dose in all patients (2 trials). See table Characteristics of excluded studies.

The 23 remaining articles described 21 RCTs that met the inclusion criteria and are described in the table Characteristics of included studies.

The 7 remaining references have not been retrieved yet (see Characteristics of studies awaiting classification).

Included studies

21 RCTs that provided data on 1,993 patients are included in the meta-analysis. In thirteen trials parallel design was used (Calvo 2006a; Glasser 2003; Hermida 2003; Hermida 2004; Hermida 2005a; Hermida 2005b; Hermida 2007; Hermida 2007a; Hermida 2008; Hermida 2008a; Hermida 2009; Hermida 2009a; Hermida 2009b) and eight used crossover design (Morgan 1997, Myburgh 1995, Neutel 2005, Nold 1998, Palatini 1992, Pechere 1998, Qiu 2003, White 1999a).

The number of participants in each trial ranged from 10 to 259. The entry criteria of the 21 included RCTs were similar with respect to DBP, requiring participants with DBP 90-115 mm Hg, but exclusion criteria varied between trials. The age ranged from 18 to 78 years. The gender mix of participants was different between trials (range 32% to 100% male). Seven trials reported ethnicity (Glasser 2003, Hermida 2003, Hermida 2004, Hermida 2005b, Neutel 2005, Qiu 2003, White 1999a), and most participants were white. Thirteen trials not reporting ethnicity were conducted in Europe or Australia (Calvo 2006a, Hermida 2005a, Hermida 2007, Hermida 2007a, Hermida 2008, Hermida 2008a, Hermida 2009, Hermida 2009a, Hermida 2009b, Morgan 1997, Nold 1998, Palatini 1992, Pechere 1998), therefore it was likely that most of the participants were white. One trial was conducted in South Africa (Myburgh 1995).

Each trial administered once-daily dose antihypertensive drug at night (6 p.m. to midnight) or in the morning (6 a.m. to noon), but the antihypertensive drug and dose used between trials were different, thus there was substantial heterogeneity observed between trials.

No trial reported all cause mortality, cardiovascular outcomes and serious adverse events.

All trials reported the changes from baseline to endpoint in 24-hour blood pressure. The data of SBP, DBP and SE were obtained from texts, figures and tables.

Three trials reported the changes in the morning blood pressure from 6 a.m. to noon with SD (Glasser 2003, Neutel 2005) and SE (White 1999a).

Ten trials reported adverse events (Calvo 2006a, Glasser 2003, Hermida 2007, Hermida 2007a, Hermida 2008, Hermida 2008a, Hermida 2009, Hermida 2009a, Hermida 2009b, Myburgh 1995).

Excluded studies

64 trials were excluded and the reasons for exclusion are reported in Characteristics of excluded studies.

Risk of bias in included studies

For the overall assessment of the risk of bias in included studies see Figure 1 and Figure 2.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

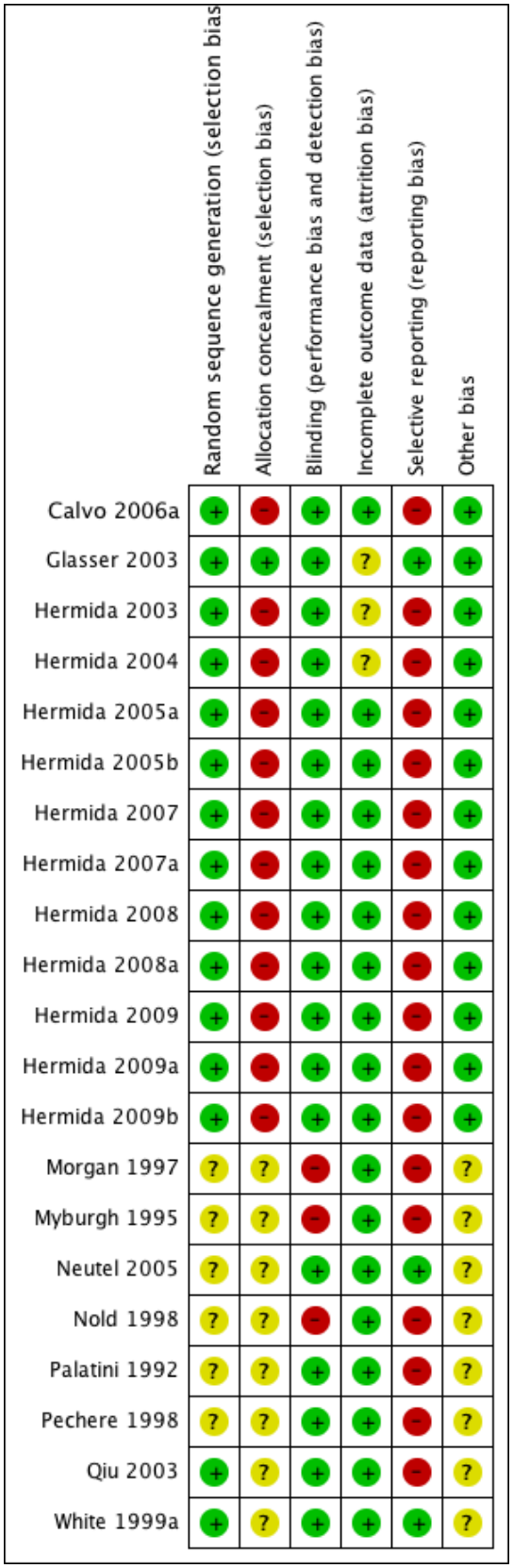
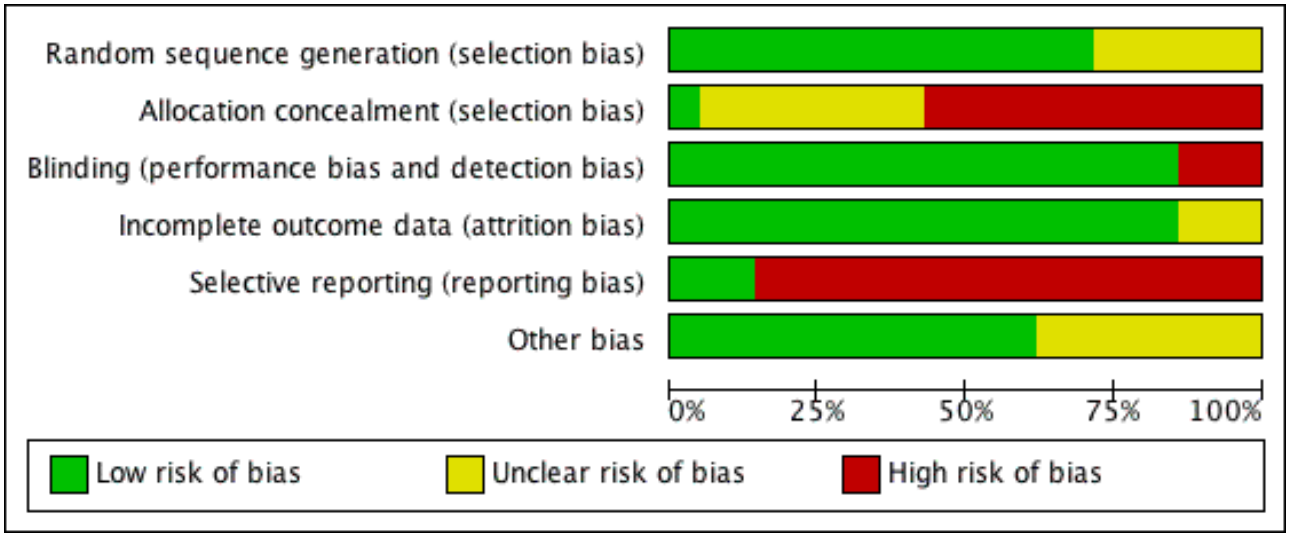


Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Although all the included trials were randomised, the quality was downgraded due to lack of allocation concealment and selective reporting as major risks of bias.

Allocation

The method of randomization was confirmed to be adequate in 15 trials (Calvo 2006a, Glasser 2003, Hermida 2003, Hermida 2004, Hermida 2005a, Hermida 2005b, Hermida 2007, Hermida 2007a, Hermida 2008, Hermida 2008a, Hermida 2009, Hermida 2009a, Hermida 2009b, Qiu 2003, White 1999a) and was not reported in the other 6 trials (Morgan 1997, Myburgh 1995, Neutel 2005, Nold 1998, Palatini 1992, Pechere 1998). Concealment of allocation was confirmed as adequate in only one trial (Glasser 2003).

Blinding

Six trials blinded both treatment providers and participants (Glasser 2003, Neutel 2005, Palatini 1992, Pechere 1998, Qiu 2003, White 1999a), twelve trials blinded investigators obtaining the BP data and outcome assessors (Calvo 2006a, Hermida 2003, Hermida 2004, Hermida 2005a, Hermida 2005b, Hermida 2007, Hermida 2007a, Hermida 2008, Hermida 2008a, Hermida 2009, Hermida 2009a, Hermida 2009b), three trials did not implement blinding (Morgan 1997, Myburgh 1995, Nold 1998).

Incomplete outcome data

Loss to follow-up was reported in all trials, but three trials did not report the distribution according to treatment group (Glasser 2003, Hermida 2003, Hermida 2004).

Selective reporting

We identified selective outcome reporting bias in nineteen trials (Calvo 2006a, Hermida 2003, Hermida 2004, Hermida 2005a, Hermida 2005b, Hermida 2007, Hermida 2007a, Hermida 2008, Hermida 2008a, Hermida 2009, Hermida 2009a, Hermida 2009b, Morgan 1997, Myburgh 1995, Nold 1998, Palatini 1992, Pechere 1998, Qiu 2003, White 1999a).

Other potential sources of bias

Eleven trials were supported by grants (Calvo 2006a, Hermida 2004, Hermida 2005a, Hermida 2007, Hermida 2007a, Hermida 2008, Hermida 2008a, Hermida 2009, Hermida 2009a. In 2 trials (Hermida 2009b, Nold 1998), conflict of interest was not declared. None of the eight crossover trials reported the carryover effects (Morgan 1997, Myburgh 1995, Neutel 2005, Nold 1998, Palatini 1992, Pechere 1998, Qiu 2003, White 1999a).

Effects of interventions

All trials reported data on BP, and 10 trials reported adverse events. Findings from these trials were aggregated in a meta-analysis. Forest plots of these results are given in Analysis 1.1, Analysis 1.2, Analysis 1.3, Analysis 1.4, Analysis 1.5, Analysis 1.6.

Mortality, cardiovascular mortality and morbidity outcomes

No RCTs that met the inclusion criteria reported data on mortality, **c**ardiovascular mortality or morbidity.

None of the trials reported serious adverse events.

Blood pressure outcomes

Change in 24-hour SBP

In general, the analysis of the overall mean difference in 24-hour SBP (Analysis 1.1) found that the evening regimen reduced 24-hour SBP by -1.71 mm Hg (95%CI -2.78 to -0.65), which was a statistically significant difference. Significant heterogeneity (I^2=85%) was observed.

For the subgroup analysis of mean difference in 24-hour SBP, evening versus morning dosing regimen, no differences were found with beta-blocker chronotherapeutic agents, ACEIs, ARBs and CCBs. Evening dosing reduced 24-hour SBP by 1.40 mm Hg (95%CI -3.60 to 6.40), -0.93 mm Hg (95%CI -3.11 to 1.24), -0.87 mm Hg (95%CI -2.12 to 0.38) and -1.64 mm Hg (95%CI -3.39 to 0.12) respectively compared with morning dosing. There were statistically significant

differences found in alpha-blockers and diuretics evening versus morning dosing regimen, evening dosing reduced 24-hour SBP by -5.10 mm Hg (95%CI -8.43 to -1.77) and -6.22 mm Hg (95%CI -9.34 to -3.10) respectively.

Change in 24-hour DBP

The analysis of mean difference in 24-hour DBP (Analysis 1.2) found that the evening regimen significantly reduced 24-hour DBP by -1.38 mm Hg (95%CI -2.13 to -0.62), but there was significant heterogeneity (I^2=85%).

For the subgroup analysis of mean difference in 24-hour DBP, statistical significant differences were observed in alpha-blockers and diuretics, evening dosing reduced 24-hour DBP by -2.70 mm Hg (95%CI -5.17 to -0.23) and -5.60 mm Hg (95%CI -6.82 to -4.38) respectively compared with morning regimen. No differences were found in evening versus morning dosing regimen with beta-blocker chronotherapeutic agents, and conventional ACEIs, ARBs and CCBs. Evening dosing reduced 24-hour DBP by 1.10 mm Hg (95%CI -2.27 to 4.47), -1.56 mm Hg (95%CI -3.18 to 0.06), -0.72 mm Hg (95%CI -1.86 to 0.43) and -0.61 mm Hg (95%CI -1.58 to 0.35) respectively compared with morning dosing.

Change in morning SBP

The analysis of mean difference in morning SBP (Analysis 1.3), based on very limited data, found no statistical difference in evening dosing versus morning dosing regimen, -1.62 mm Hg (95%CI -4.19 to 0.95, I^2=59%). For the subgroup analysis of mean difference in morning SBP, there was statistical difference found in CCBs evening versus conventional morning dosing, -2.68 mm Hg (95%CI -4.46 to -0.89); no statistical difference was found with beta-blocker chronotherapeutic formulation versus conventional medication, 1.50 mm Hg (95%CI -2.51 to 5.15).

Change in morning DBP

The analysis of mean difference in morning DBP (Analysis 1.4), based on very limited data, found that evening dosing did not significantly lower morning DBP compared with conventional dosing regimen, -1.21 mm Hg (95%CI -3.28 to 0.86, I^2=66%). There was no statistical differences found in CCBs evening versus conventional morning dosing, -1.87 mm Hg (95%CI -4.32 to 0.58). There was no statistically significant difference with beta-blocker chronotherapeutic formulation versus conventional medication, 0.40 mm Hg (95% CI -2.09 to 2.89).

Adverse events

Five parallel trials (Calvo 2006a, Glasser 2003, Hermida 2008, Hermida 2008a, Hermida 2009a) reported overall adverse effects and six trials (Hermida 2007, Hermida 2007a, Hermida 2008, Hermida 2009, Hermida 2009a, Hermida 2009b) reported withdrawals due to adverse events.

One crossover trial (Myburgh 1995) reported three patient withdrawals due to adverse events. No patient was reported to have any side effects during the entire study period in the crossover trial (Palatini 1992) and the remaining six crossover studies (Morgan 1997, Neutel 2005, Nold 1998, Pechere 1998, Qiu 2003, White 1999a) did not report whether participants suffered any adverse effects.

The meta-analysis of 5 parallel trials showed that there was no statistically significant difference between evening and conventional dosing regimen in the incidence of overall adverse events (RR 0.78, 95%CI: 0.37 to 1.65, I^2=59%, Analysis 1.5) and withdrawals due to adverse events (RR 0.53, 95%CI: 0.26 to 1.07, I^2=0%, Analysis 1.6). For the subgroup analysis of overall adverse events, similar results were found for ACEIs, CCBs and diuretics evening compared with morning dosing regimen (RR 0.50, 95%CI: 0.10 to 2.63; RR = 0.52, 95%CI: 0.11 to 2.49; RR = 1.66, 95%CI: 0.56 to 4.90; respectively); for withdrawal due to adverse events, no differences were found in ACEIs, ARBs and CCBs evening versus morning dosing regimen (RR = 1.00, 95%CI: 0.06 to 15.62; RR = 0.30, 95%CI: 0.06 to 1.41; RR = 0.59, 95%CI: 0.26 to 1.33; respectively).

Funnel plot analysis

Funnel plots of 24-hour SBP and DBP outcome data indicate evidence of publication bias (see Figure 3, Figure 4).

Figure 3. Funnel plot of comparison: 1 evening versus morning dosing regimen, outcome: 1.1 24 h mean systolic blood pressure.

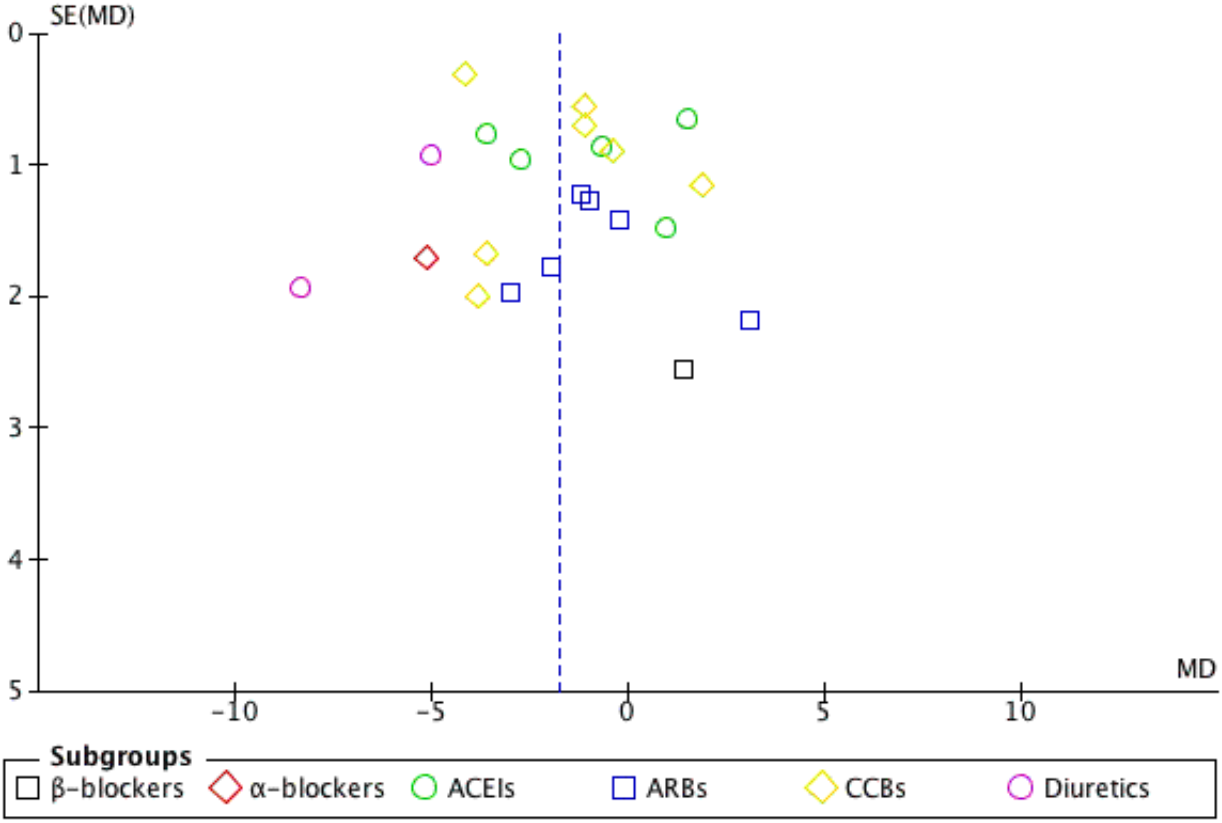
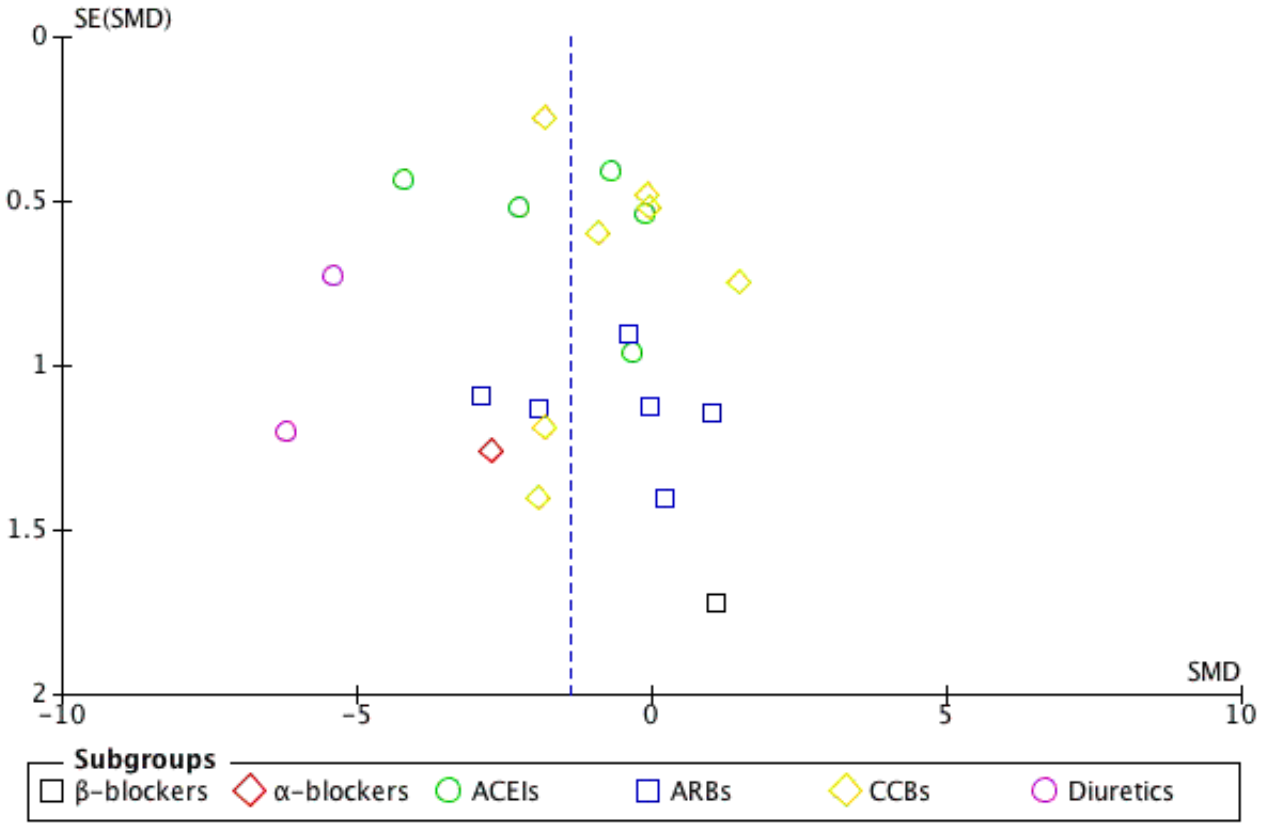


Figure 4. Funnel plot of comparison: 1 evening versus morning dosing regimen, outcome: 1.2 24 h mean diastolic blood pressure



DISCUSSION

Summary of main results

No eligible studies evaluated mortality or morbidity for the six traditional antihypertensive drug classes morning versus evening once daily monotherapy regimens.

There were no significant differences in overall adverse effects and withdrawals due to adverse effects among the two dosing regimens. Subgroup analysis of overall adverse events found no differences with ACEIs, CCBs and diuretic drug class evening versus morning dosing regimen; for the withdrawal profile, similar results were found with ACEIs, ARBs and CCBs between the two dosing regimens.

This review provided very limited morning BP data for beta-blockers and CCBs. Adverse events data (ACEIs, CCBs and diuretics) and withdrawals due to adverse effect (ACEIs, ARBs and CCBs) were reported, but no serious adverse events data for all the six conventional class antihypertensive agents were reported.

In a subgroups analysis of 24-hour SBP, no differences were found for beta-blockers, ACEIs, ARBs and CCBs evening versus morning dosing regimen. Statistically significant differences were found between evening versus morning dosing regimen for two drug classes, alpha-blockers (limited to one trial data Hermida 2004) and diuretics (limited to 2 trials Calvo 2006a and Hermida 2008a).

In a subgroups analysis of 24-hour DBP, no differences were found for beta-blockers, ACEIs, ARBs and CCBs evening versus morning dosing regimen. Statistically significant differences were found between evening versus morning dosing regimen for alpha-blockers (limited to one trial Hermida 2004) and diuretics (limited to 2 trials Calvo 2006a and Hermida 2008a).

Quality of the evidence

Most trials had risks of bias in at least two of several key criteria. One trial had risk of bias due to incomplete outcome data (Glasser 2003). See Figure 1

Nineteen of the 21 included studies were double-blind, involving 97% (N=1,928) of the entire studied population. Fifteen trials reported adequate sequence generation. However, only one trial reported adequate concealment of allocation [N=205, 11% (205/1993) of total randomized participants], so the number of patients randomized with adequate concealment of allocation was very low.

Three of the 21 included studies had incomplete outcome data. However, risk of bias due to selective reporting was found in 19 of the 21 included studies had a bias.

Thirteen trials (N=1729, 87%) had no other bias.

See Figure 1 and Figure 2 for a graphic representation of the overall risks of bias detected in the 21 included studies.

Funnel plot analysis

We performed a funnel plot analysis and found evidence of publication bias since the trials in lower right hand and left hand area in the funnel plot are missing (see Figure 3, Figure 4).

AUTHORS' CONCLUSIONS

Implications for practice

Based on data for 6 classes of antihypertensive drugs, evening administration lowered 24-hour SBP by 1.61 mm Hg and 24-hour DBP by 1.23 mm Hg. In particular the alpha-blocker doxazosin GITS (4 mg/day) and the diuretic torasemide (5 mg/day) evening administration reduced 24-hour SBP by 5.10 and 6.24 mm Hg respectively and 24-hour DBP by 2.70 and 5.95 mm Hg respectively. The clinical relevance of this decrease is not known, since very limited data has been reported for morning SBP and DBP, and mortality and morbidity data have not been reported. There were no significant differences in overall adverse effects and withdrawals due to adverse effects among the two regimens.

This systematic review found that nighttime dosing of antihypertensive drugs is more effective than morning administration to lower 24-hour BP, but did not find adequate data to determine which of the two regimens may have more beneficial effects on cardiovascular outcomes or adverse events.

Implications for research

The short-term trials conducted to date, which report the mean BP lowering efficacy as a surrogate outcome, are not adequate to establish which of the two dosing regimens may be better. Large double-blind randomized controlled trials are needed to evaluate the administration time-related -effects of different antihypertensive drug classes given as monotherapy or as first line drugs with stepped up therapy on mortality and cardiovascular morbidity, with long-term follow up data of at least 3 to 5 years duration.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Calvo 2006a

Methods	prospective randomized open-label, blinded endpoint, parallel-group trial. Subjects ingested the single daily tablet of torasemide for 6 weeks. Baseline similarity: age, height, eight, BMI, waist and hip perimeters, BP, laboratory chemistry parameters sample size calculation:not reported
Participants	Country: Spain Number randomised: 58 Mean age: 48.7±11.9(SD) years gender: 25 men, 33 women. Ethnicity: not reported Inclusion Criteria: age>18 years, conventional SBP between 140 and 179 mm Hg or DBP between 90 and 109 mm Hg, and ABPM diurnal mean >135/85 mm Hg, or the nocturnal mean > 120/70 mm Hg. Exclusion criteria: grade 3 essential hypertension, shift workers, heavy drinkers, and cardiovascular disorders
Interventions	torasemide (5 mg od) on awakening: N=30 torasemide (5 mg od) at bedtime:N=28
Outcomes	**Mortality**: not reported **Morbidity:** not reported **Blood Pressure data**:24h BP change by 48h ABPM, data was obtained from graph and text (fig 5 on page 728) **Adverse Events:** overall adverse events
Notes	supported in part by grants from Xunta de Galicia (PGIDIT03-PXIB-32201PR), Hospital Clınico Universitario de Santiago and University of Vigo

Calvo 2006a *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computerized random-number generator
Allocation concealment (selection bias)	High risk	one member of the research team used a list of random numbers
Blinding (performance bias and detection bias) All outcomes	Low risk	investigator obtaining the BP measurements, outcome assessors blinded. Benefits of the PROBE design and its validity compared with double-blind, placebo-controlled trials in assessing antihypertensive efficacy based on blinded ABPM measurements have been documented previously (Smith 2003)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were reported. 6 lost to follow-up for no second ABPM available, 3 in awakening group, 3 in bedtime group.
Selective reporting (reporting bias)	High risk	Morning SBP, DBP, serious adverse events were not reported.
Other bias	Low risk	This trial was a part of MAPEC (http://www.clinicaltrials.gov/ct2/show/NCT00295542?term=NCT00295542). The funding body has no role in the study design, analysis and interpretation of data, writing of the reports, or the decision to submit articles to publication (Hermida 2007b)

Glasser 2003

Methods	multicenter (N=39), double-blind, parallel-group, dose-response, placebo-controlled, randomized study. The study consisted of an initial screening period followed by a 3- to 4-week single-blind, placebo run-in period, and 7-week double-blind active treatment period. Baseline similarity: age, height, weight, gender, ethnicity, BP, HR Sample size calculation: reported
Participants	Country: the United States Number randomised: 478 age range: 18-70 years gender: 303 men, 175 women; relevant treatment group: 130 men, 75 women ethnicity: 302 White, 132 African-American, 44 other; relevant treatment group: 133 White, 56 African-American, 16 other inclusion criteria: seated SBP <200 mm Hg, 100 mm Hg≤mean seated DBP≤114 mm Hg, and 90 mm Hg ≤mean daytime (8AM-4PM) DBP ≤114 mm Hg exclusion criteria: recent history of serious cardiovascular or cerebrovascular events, secondary hypertension, any serious chronic or uncontrolled medical conditions, nightshift workers and sensitivity to diltiazem
Interventions	placebo group:N=69 GRD 120 mg PM group: N=67 GRD 240 mg PM group: N=68 GRD 360 mg AM group: N=102 GRD 360 mg PM group: N=103 GRD 540 mg PMgroup : N=69 The relevant treatment groups for this review are following two arms:

Glasser 2003 *(Continued)*

	GRD 360 mg AM group, GRD was taken each morning at 8 AM +/-1 h (N=102) GRD 360 mg PM group, GRD was taken each evening at 10 PM +/- 1h (N=103)
Outcomes	**Mortality**: not reported **Morbidity:** not reported **Blood Pressure data**: morning BP (6AM-noon) change by 24 h ABPM (table 2 on page 55); 24h BP change by 24h ABPM (table 2 on page 55) **Adverse Events:**Overall adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	central telephone
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	clinicians, patients blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All participants (N=478) were reported. 49 withdrawals are explained. 3.2% of GRD-treated patients and 4.3% of placebo treated patients withdrawal due to adverse event, the other reasons for withdrawal included noncompliance, withdrawal of consent, and lack of efficacy, but distribution according to which treatment group was not reported.
Selective reporting (reporting bias)	Low risk	All outcomes were not reported.
Other bias	Low risk	None identified

Hermida 2003

Methods	prospective, randomized, open-label, blinded end point, parallel-group trial. 2- to 4-week washout period and 3 months timed active treatment . Baseline similarity: age, height, weight, BMI, waist and hip perimeters, SBP, and DBP, laboratory chemistry variables Sample size calculation: not reported
Participants	Country: Spain Number randomised:90 Mean age: 49.0±14.3(SD) years gender: 30 men, 60 women Ethnicity: White Inclusion Criteria: conventional SBP between 140 and 179 mm Hg, or DBP between 90 to 109 mm Hg, and ABPM 24 hour mean SBP/DBP > 130/80 mm Hg, diurnal mean >135/85 mm Hg, or the nocturnal mean > 120/70 mm Hg.

Hermida 2003 *(Continued)*

	Exclusion criteria: shift workers, heavy drinkers, smokers, and heavy exercisers, severe arterial hypertension, secondary arterial hypertension, cardiovascular disorders, including angina, heart failure, stroke, nephropathy, retinopathy, prior myocardial infarction or coronary revascularization.
Interventions	valsartan 160 mg/d awakening: N=46 valsartan 160 mg/d bedtime: N=44
Outcomes	**Mortality**: not reported **Morbidity:** not reported **Blood Pressure data**:24h BP change by 48h ABPM, data was obtained from graph and text (fig 3 on page 288) **Adverse Events:** not reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computerized random-number generator
Allocation concealment (selection bias)	High risk	"Assignment of subjects to treatment groups was done by 1 member of the research team, according to the order of recruitment, following an allocation table constructed by a computerized random-number generator."
Blinding (performance bias and detection bias) All outcomes	Low risk	investigator obtaining the BP measurements and outcome assessors blinded. Benefits of the PROBE design and its validity compared with double-blind, placebo-controlled trials in assessing antihypertensive efficacy based on blinded ABPM measurements have been documented previously (Smith 2003).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All participants were reported. 6 subjects missing ABPM data were eliminated, 3 subjects discontinued timed treatment or they failed to return for the second ABPM at the end of treatment, but distribution according to group not reported
Selective reporting (reporting bias)	High risk	Morning SBP, DBP were not reported.
Other bias	Low risk	None identified

Hermida 2004

Methods	prospective randomized open-label, blinded endpoint, parallel-group trial. 3 months timed active treatment Baseline similarity: age, height, weight, BMI, waist and hip perimeters, SBP, DBP,laboratory chemistry variables sample size calculation: not reported
Participants	Country: Spain Number randomised:91 Mean age: 56.7±11.2(SD) years gender: 49 men, 42 women; relevant treatment groups: 27 men, 12 women

Hermida 2004 *(Continued)*

	Ethnicity: Caucasian Inclusion Criteria: conventional SBP between 140 and 179 mm Hg, or DBP between 90 to 109 mm Hg, and ABPM 24 hour mean SBP/DBP > 130/80 mm Hg, diurnal mean >135/85 mm Hg, or the nocturnal mean > 120/70 mm Hg. Exclusion criteria: shift workers, heavy drinkers, smokers, and heavy exercisers, severe arterial hypertension, secondary arterial hypertension, angina, heart failure, stroke, nephropathy, retinopathy, prior myocardial infarction or coronary revascularization.
Interventions	morning monotherapy: a single daily tablet of doxazosin GITS(4 mg/day) was taken in the morning (N=20) bedtime monotherapy: a single daily tablet of doxazosin GITS(4 mg/day) was taken at bedtime (N=19) morning polytherapy: N=24 bedtime polytherapy: N=28 polytherapy group allowed combination of antihypertensive medications was restricted to angiotensin receptor blockers plus either a diuretic or calcium channel blocker, and ACE inhibitors plus either a diuretic or calcium channel blocker, each group received a single daily tablet of doxazosin GITS(4 mg/day), so the polytherapy arms were excluded for this review.
Outcomes	**Mortality**: not reported **Morbidity:** not reported **Blood Pressure data**:24h BP change by 48h ABPM, data was obtained from graph and text (fig 5 on page 290) **Adverse Events:** not reported
Notes	supported in part by grants from Xunta de Galicia (PGIDIT03-PXIB-32201PR), and Vicerrectorado de Investigacion, University of Vigo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computerized random-number generator
Allocation concealment (selection bias)	High risk	one member of the research team used a list of random numbers
Blinding (performance bias and detection bias) All outcomes	Low risk	investigator obtaining the BP measurements, outcome assessors blinded. Benefits of the PROBE design and its validity compared with double-blind, placebo-controlled trials in assessing antihypertensive efficacy based on blinded ABPM measurements have been documented previously (Smith 2003)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All participants were reported. "BP profiles of seven subjects, originally randomized but not incorporated in this efficacy evaluation, were eliminated because of missing ABPM data", but distribution according to group was not reported
Selective reporting (reporting bias)	High risk	Morning SBP, DBP were not reported.
Other bias	Low risk	This trial was a part of MAPEC (http://www.clinicaltrials.gov/ct2/show/NCT00295542?term=NCT00295542). The funding body has no role in the study design, analysis and interpretation of data, writing of the reports, or the decision to submit articles to publication (Hermida 2007b).

Hermida 2005a

Methods	prospective randomized open-label, blinded endpoint, parallel-group trial. 3 months of intervention Baseline similarity: age, height, weight, BMI, waist and hip perimeters, SBP, DBP,laboratory chemistry variables sample size calculation:not reported
Participants	Country: Spain Number randomised: 105,100 completed Mean age: 68.2±4.9(SD) years gender: 34 men, 66 women. Ethnicity: not reported Inclusion Criteria: untreated, age≥60years, conventional SBP between 140 and 179 mm Hg or DBP between 90 and 109 mm Hg, and ABPM diurnal mean SBP/DBP>135/85 mm Hg, or the nocturnal mean > 120/70 mm Hg. Exclusion criteria: shift workers, heavy drinkers, smokers, heavy exercisers, severe arterial or secondary arterial hypertension, nephropathy and retinopathy and/or cardiovascular disorders.
Interventions	valsartan (160mg/d) on awakening: N=53 valsartan monotherapy (160mg/d) at bedtime:N=52
Outcomes	**Mortality**: not reported **Morbidity:** not reported **Blood Pressure data**:24h BP change by 48h ABPM, data was obtained from graph and text (fig 5 on page 770) **Adverse Events:** not reported
Notes	supported in part by grants from Xunta de Galicia (PGIDIT03-PXIB-32201PR), and Vicerrectorado de Investigacion, University of Vigo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computerized random-number generator
Allocation concealment (selection bias)	High risk	one member of the research team use of a list of random numbers
Blinding (performance bias and detection bias) All outcomes	Low risk	investigator obtaining the BP measurements and outcome assessors blinded. Benefits of the PROBE design and its validity compared with double-blind, placebo-controlled trials in assessing antihypertensive efficacy based on blinded ABPM measurements have been documented previously (Smith 2003)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were reported. 5 subjects were eliminated for second ABPM, 3 in the morning treatment and 2 in bedtime treatment.
Selective reporting (reporting bias)	High risk	Morning SBP, DBP were not reported.
Other bias	Low risk	This trial was a part of MAPEC (http://www.clinicaltrials.gov/ct2/show/NCT00295542?term=NCT00295542). "The funding body has no role in the study

Hermida 2005a *(Continued)*

	design, analysis and interpretation of data, writing of the reports, or the decision to submit articles to publication (Hermida 2007b)".

Hermida 2005b

Methods	prospective randomized open-label, blinded endpoint, parallel-group trial. After 2-4 week washout period, subjects received timed active treatment for 3 months Baseline similarity: age, height, eight, BMI, waist and hip perimeters, BP, laboratory chemistry variables sample size calculation:not reported
Participants	Country: Spain Number randomised: 152,148 completed Mean age: 53.0±12.6(SD) years gender: 50 men, 98 women. Ethnicity: white Inclusion Criteria: conventional SBP between 140 and 179 mm Hg or DBP between 90 and 109 mm Hg, and ABPM 24 hour mean SBP/DBP > 130/80 mm Hg, diurnal mean >135/85 mm Hg, or the nocturnal mean > 120/70 mm Hg. Exclusion criteria: shift workers, heavy drinkers, smokers, heavy exercisers, severe arterial or secondary arterial hypertension, nephropathy and retinopathy and/or cardiovascular disorders.
Interventions	valsartan monotherapy (160mg od) on awakening: N=75 valsartan monotherapy (160mg od) at bedtime:N=77
Outcomes	**Mortality**: not reported **Morbidity:** not reported **Blood Pressure data**:24h BP change by 48h ABPM, data was obtained from graph and text (fig 4 on page 1919) **Adverse Events:** not reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computerized random-number generator
Allocation concealment (selection bias)	High risk	one member of the research team used a list of random numbers
Blinding (performance bias and detection bias) All outcomes	Low risk	investigator obtaining the BP measurements, outcome assessors blinded. Benefits of the PROBE design and its validity compared with double-blind, placebo-controlled trials in assessing antihypertensive efficacy based on blinded ABPM measurements have been documented previously (Smith 2003)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were reported. "Baseline blood pressure profiles of four additional subjects (three originally assigned to morning treatment and one to bedtime treatment) were eliminated because the patients failed to return for the second ABPM at the end of treatment."

Hermida 2005b *(Continued)*

Selective reporting (reporting bias)	High risk	Morning SBP, DBP were not reported.
Other bias	Low risk	None identified

Hermida 2007

Methods	prospective randomized open-label, blinded endpoint, parallel-group trial. Subjects ingested the single daily tablet of nifedipine GITS (30 mg/day) for eight weeks. After this first stage of timed treatment, uncontrolled patients were asked to remain in the trial and be up-titrated to 60 mg/day nifedipine GITS for another eight weeks at the same circadian time. Baseline similarity: age, height, eight, BMI, waist and hip perimeters, BP, laboratory chemistry variables sample size calculation:not reported
Participants	Country: Spain Number randomised: 90, 80 completed Mean age: 52.1±10.7(SD) years gender: 36 men, 44 women. Ethnicity: not reported Inclusion Criteria: conventional SBP between 140 and 179 mm Hg or DBP between 90 and 109 mm Hg, and ABPM 24 hour mean SBP/DBP > 130/80 mm Hg, diurnal mean >135/85 mm Hg, or the nocturnal mean > 120/70 mm Hg. Exclusion criteria: shift workers, heavy drinkers, smokers, heavy exercisers, severe arterial or secondary arterial hypertension, nephropathy and retinopathy and/or cardiovascular disorders
Interventions	nifedipine GITS (30 mg od) on awakening: N=43 nifedipine GITS (30 mg od) at bedtime:N=47 nifedipine GITS (60 mg od) on awakening:N=21 nifedipine GITS (60 mg od) at bedtime:N=19
Outcomes	**Mortality**: not reported **Morbidity:** not reported **Blood Pressure data**: 24h BP change by 48h ABPM, data was obtained from graph and text (fig 6 on page 485) **Adverse Events:** withdrawals due to adverse events
Notes	supported in part by grants from Ministerio de Educacio´n y Ciencia, Xunta de Galicia , Quımica Farmaceutica Bayer, Hospital Clınico Universitario de Santiago, and University of Vigo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computerized random-number generator
Allocation concealment (selection bias)	High risk	one member of the research team use of a list of random numbers

Hermida 2007 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	investigator obtaining the BP measurements, outcome assessors blinded. Benefits of the PROBE design and its validity compared with double-blind, placebo-controlled trials in assessing antihypertensive efficacy based on blinded ABPM measurements have been documented previously (Smith 2003)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data on all participants were reported. 90 randomised, 80 completed. At the first stage of timed treatment, 6 lost to follow-up for no second ABPM available, 1 in daytime group, 5 in bedtime group, 4 withdrawn due to adverse effects, 3 in daytime group, 1 in bedtime group;At the second stage of timed treatment (uncontrolled BP, N=40), 5 discontinued because of adverse effects, 3 in daytime group, 2 in bedtime group
Selective reporting (reporting bias)	High risk	Morning SBP, DBP, overall adverse events, serious adverse events were not reported.
Other bias	Low risk	This trial was a part of MAPEC (http://www.clinicaltrials.gov/ct2/show/NCT00295542?term=NCT00295542). "The funding body has no role in the study design, analysis and interpretation of data, writing of the reports, or the decision to submit articles to publication (Hermida 2007b)".

Hermida 2007a

Methods	prospective randomized open-label, blinded endpoint, parallel-group trial.Subjects ingested the single daily tablet of telmisartan (80 mg/day) for 12 weeks Baseline similarity: age, height, eight, BMI, waist and hip perimeters, BP, laboratory chemistry variables sample size calculation: reported
Participants	Country: Spain Number randomised: 231, 215 completed Mean age: 46.4±12.0(SD) years gender: 114 men, 101 women. Ethnicity: not reported Inclusion Criteria: age≥18 years, conventional SBP between 140 and 179 mm Hg or DBP between 90 and 109 mm Hg, and ABPM diurnal mean >135/85 mm Hg, or the nocturnal mean > 120/70 mm Hg. Exclusion criteria: shift workers, heavy drinkers, smokers, heavy exercisers, severe arterial or secondary arterial hypertension, type 1 diabetes, and cardiovascular disorders
Interventions	telmisartan (80mg od) on awakening: N=117 telmisartan (80mg od) at bedtime: N=114
Outcomes	**Mortality**: not reported **Morbidity:** not reported **Blood Pressure data**: 24h BP change by 48h ABPM, data was obtained from graph and text (fig 2 on page 720) **Adverse Events:** withdrawals due to adverse events
Notes	supported in part by grants from Ministerio de Educacion y Ciencia, Xunta de Galicia, Hospital Clınico Universitario de Santiago, and University of Vigo

Risk of bias

Hermida 2007a *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computerized random-number generator
Allocation concealment (selection bias)	High risk	one member of the research team use of a list of random numbers
Blinding (performance bias and detection bias) All outcomes	Low risk	investigator obtaining the BP measurements, outcome assessors blinded. Benefits of the PROBE design and its validity compared with double-blind, placebo-controlled trials in assessing antihypertensive efficacy based on blinded ABPM measurements have been documented previously (Smith 2003)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data on all participants were reported. 231 randomised, 215 completed. 11 lost to follow-up for no second ABPM available, 6 in daytime group, 5 in bedtime group; 5 withdrawn due to adverse effects, 4 in daytime group, 1 in bedtime group
Selective reporting (reporting bias)	High risk	Morning SBP, DBP were not reported. Compliance was measured but data was not provided
Other bias	Low risk	This was an investigator-promoted independent research.

Hermida 2008

Methods	prospective randomized open-label, blinded endpoint, parallel-group trial. Subjects ingested the single daily tablet of nifedipine GITS (30 mg/day) for 8 weeks. Baseline similarity: age, height, eight, BMI, waist perimeters, BP,HR, laboratory chemistry variables sample size calculation: reported
Participants	Country: Spain Number randomised: 198, 180 completed Mean age: 52.5±10.7(SD) years gender: 86 men, 94 women. Ethnicity: not reported Inclusion Criteria: untreated, age≥18 years, conventional SBP between 140 and 179 mm Hg or DBP between 90 and 109 mm Hg, and ABPM diurnal mean >135/85 mm Hg, or the nocturnal mean > 120/70 mm Hg. Exclusion criteria: shift workers, heavy drinkers, smokers, heavy exercisers, severe arterial or secondary arterial hypertension, type 1 diabetes, and cardiovascular disorders
Interventions	nifedipine GITS (30 mg od) on awakening: N=97 nifedipine GITS (30 mg od) at bedtime:N=101
Outcomes	**Mortality**: not reported **Morbidity:** not reported **Blood Pressure data**: 24h BP change by 48h ABPM, data was obtained from graph and text (fig 3 on page 952) **Adverse Events:** overall adverse events; withdrawals due to adverse events
Notes	supported in part by grants from Ministerio de Educación y Ciencia, Xunta de Galicia, Hospital Clınico Universitario de Santiago, and University of Vigo.

Hermida 2008 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computerized random-number generator
Allocation concealment (selection bias)	High risk	one member of the research team use of a list of random numbers
Blinding (performance bias and detection bias) All outcomes	Low risk	investigator obtaining the BP measurements, outcome assessors blinded. Benefits of the PROBE design and its validity compared with double-blind, placebo-controlled trials in assessing antihypertensive efficacy based on blinded ABPM measurements have been documented previously (Smith 2003)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were reported. 8 lost to follow-up for no second ABPM available, 3 in daytime group, 5 in bedtime group; 10 withdrawn due to adverse effects, 6 in daytime group, 4 in bedtime group
Selective reporting (reporting bias)	High risk	Morning SBP, DBP, serious adverse events were not reported.
Other bias	Low risk	The authors declared no conflict of interest

Hermida 2008a

Methods	prospective randomized open-label, blinded endpoint, parallel-group trial. 6 weeks of intervention Baseline similarity: age, height, eight, BMI, waist perimeters, BP,HR, laboratory chemistry variables sample size calculation: reported
Participants	Country: Spain Number randomised: 121, 113 completed Mean age: 51.7±10.67(SD) years gender: 44 men, 69 women. Ethnicity: not reported Inclusion Criteria: untreated, age≥18 years, conventional SBP between 140 and 179 mm Hg or DBP between 90 and 109 mm Hg, and ABPM awake BP of mean ≥135/85 mm Hg, or asleep mean ≥120/70 mm Hg. Exclusion criteria: pregnant women, shift workers, heavy drinkers, smokers, heavy exercisers, severe arterial or secondary arterial hypertension, type 1 diabetes, and cardiovascular disorders
Interventions	torasemide (5 mg od) on awakening: N=61 torasemide (5 mg od) at bedtime:N=60
Outcomes	**Mortality**: not reported **Morbidity:** not reported **Blood Pressure data**: 24h BP change by 48h ABPM, data was obtained from graph and text (fig 3 on page 961) **Adverse Events:** overall adverse events
Notes	supported in part by grants from Ministerio de Educación y Ciencia, Xunta de Galicia, Hospital Clınico Universitario de Santiago, and University of Vigo.

Hermida 2008a *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computerized random-number generator
Allocation concealment (selection bias)	High risk	one member of the research team use of a list of random numbers
Blinding (performance bias and detection bias) All outcomes	Low risk	investigator obtaining the BP measurements, outcome assessors blinded. Benefits of the PROBE design and its validity compared with double-blind, placebo-controlled trials in assessing antihypertensive efficacy based on blinded ABPM measurements have been documented previously (Smith 2003)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were reported. 8 lost to follow-up for no second ABPM available, 4 in awakening group, 4 in bedtime group
Selective reporting (reporting bias)	High risk	Morning SBP, DBP, serious adverse events were not reported. Compliance was measured but data was not provided.
Other bias	Low risk	"The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper".

Hermida 2009

Methods	prospective randomized open-label, blinded endpoint, parallel-group trial. 3 months of intervention Baseline similarity: age, height, eight, BMI, waist perimeters, BP,HR, laboratory chemistry variables sample size calculation: reported
Participants	Country: Spain Number randomised: 144, 133 completed Mean age: 45.5±11.9(SD) years(awakening),47.6±12.7(SD) years (bedtime) gender: 43 men, 90 women. Ethnicity: not reported Inclusion Criteria: untreated, age≥18 years, conventional SBP between 140 and 179 mm Hg or DBP between 90 and 109 mm Hg, and ABPM awake BP of mean ≥135/85 mm Hg, or asleep mean ≥120/70 mm Hg. Exclusion criteria: pregnant women, shift workers, heavy drinkers, smokers, heavy exercisers, severe arterial or secondary arterial hypertension, type 1 diabetes, and cardiovascular disorders
Interventions	olmesartan (20 mg od) on awakening: N=73 olmesartan (20 mg od) at bedtime:N=71
Outcomes	**Mortality**: not reported **Morbidity:** not reported **Blood Pressure data**: 24h BP change by 48h ABPM, data was obtained from graph and text (fig 4 on page 72) **Adverse Events:** withdrawals due to adverse events

Hermida 2009 *(Continued)*

Notes	supported in part by grants from Ministerio de Educación y Ciencia, Xunta de Galicia, and University of Vigo.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computerized random-number generator
Allocation concealment (selection bias)	High risk	one member of the research team use of a list of random numbers
Blinding (performance bias and detection bias) All outcomes	Low risk	investigator obtaining the BP measurements, outcome assessors blinded. Benefits of the PROBE design and its validity compared with double-blind, placebo-controlled trials in assessing antihypertensive efficacy based on blinded ABPM measurements have been documented previously (Smith 2003)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data on all participants were reported. 7 lost to follow-up for no second ABPM available, 3 in daytime group, 4 in bedtime group; 4 withdrawn due to adverse effects, 3 in daytime group, 1 in bedtime group
Selective reporting (reporting bias)	High risk	Morning SBP, DBP were not reported.
Other bias	Low risk	"The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper".

Hermida 2009a

Methods	prospective randomized open-label, blinded endpoint, parallel-group trial. 6 weeks of intervention Baseline similarity: age, BP,HR sample size calculation: reported
Participants	Country: Spain Number randomised: 120, 115 completed Mean age: 46.7±11.2(SD) years gender: 52 men, 63 women. Ethnicity: not reported Inclusion Criteria: untreated, age≥18 years, conventional SBP between 140 and 179 mm Hg or DBP between 90 and 109 mm Hg, and ABPM awake BP of mean ≥135/85 mm Hg, or asleep mean ≥120/70 mm Hg. Exclusion criteria: pregnant women, shift workers, heavy drinkers, smokers, heavy exercisers, severe arterial or secondary arterial hypertension, type 1 diabetes, and cardiovascular disorders
Interventions	ramipril (5 mg od) on awakening: N=60 ramipril (5 mg od) at bedtime:N=60
Outcomes	**Mortality**: not reported **Morbidity:** not reported **Blood Pressure data**: 24h BP change by 48h ABPM, data was obtained from graph and text (fig 3 on 44) **Adverse Events:** overall adverse events; withdrawals due to adverse events

Hermida 2009a *(Continued)*

Notes	supported in part by grants from Ministerio de Educación y Ciencia, King Pharmaceuticals, Xunta de Galicia, and University of Vigo.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computerized random-number generator
Allocation concealment (selection bias)	High risk	one member of the research team use of a list of random numbers (Hermida 2007b)
Blinding (performance bias and detection bias) All outcomes	Low risk	investigator obtaining the BP measurements, outcome assessors blinded. Benefits of the PROBE design and its validity compared with double-blind, placebo-controlled trials in assessing antihypertensive efficacy based on blinded ABPM measurements have been documented previously (Smith 2003)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were reported. 3 lost to follow-up for no second ABPM available, 1 in daytime group, 2 in bedtime group; 2 withdrawn due to adverse effects, 1 in daytime group, 1 in bedtime group
Selective reporting (reporting bias)	High risk	Morning SBP, DBP, serious adverse events were not reported.
Other bias	Low risk	none conflicts of interest

Hermida 2009b

Methods	prospective randomized open-label, blinded endpoint, parallel-group trial. 8 weeks of intervention Baseline similarity: age, BP,HR sample size calculation: reported
Participants	Country: Spain Number randomised: 259, 238completed Mean age: 53.3±11.4(SD) years gender: 108 men, 130 women. Ethnicity: not reported Inclusion Criteria: untreated, age≧18 years, conventional SBP between 140 and 179 mm Hg or DBP between 90 and 109 mm Hg, and ABPM awake BP of mean ≧135/85 mm Hg, or asleep mean ≧120/70 mm Hg. Exclusion criteria: pregnant women, shift workers, heavy drinkers, smokers, heavy exercisers, severe arterial or secondary arterial hypertension, type 1 diabetes, and cardiovascular disorders
Interventions	nifedipine GITS (30 mg od) on awakening: N=129 nifedipine GITS (30 mg od) at bedtime:N=130
Outcomes	**Mortality**: not reported **Morbidity:** not reported **Blood Pressure data**:24h BP change by 48h ABPM, data was obtained from graph and text (fig 2 on 157) **Adverse Events:** withdrawals due to adverse events

Hermida 2009b *(Continued)*

Notes	supported in part by grants from Ministerio de Educación y Ciencia, Xunta de Galicia, and University of Vigo.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computerized random-number generator
Allocation concealment (selection bias)	High risk	one member of the research team use of a list of random numbers (Hermida 2007b)
Blinding (performance bias and detection bias) All outcomes	Low risk	investigator obtaining the BP measurements, outcome assessors blinded. Benefits of the PROBE design and its validity compared with double-blind, placebo-controlled trials in assessing antihypertensive efficacy based on blinded ABPM measurements have been documented previously (Smith 2003)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were reported. 11 lost to follow-up for no second ABPM available, 5 in daytime group, 6 in bedtime group; 10 withdrawn due to adverse effects, 6 in daytime group, 4 in bedtime group
Selective reporting (reporting bias)	High risk	Morning SBP, DBP were not reported.
Other bias	Low risk	none conflicts of interest

Morgan 1997

Methods	randomised crossover trial. After 4 weeks placebo run-in period, patients received perindopril in the morning and at bedtime each for 4 weeks sample size calculation: not stated. carryover effects: not reported no washout period between treatment arms
Participants	Country: Australia Number randomised:20, 20 completed Age range: 33-78 yeas mean age: 68±5 years gender: 20 male Ethnicity: not reported inclusion criteria: seated DBP 95-110 mm Hg, less than 5 mm Hg difference between the two values, and mean 24 h DBP>85 mm Hg. exclusion criteria: clinic SBP >220 mm Hg, had a history of acute cerebrovascular or coronary events within the preceding 6 months, creatinine > 0.16 mmol/l, and liver function test results 50% greater than the normal range.
Interventions	4 mg od perindopril at 0900h or at 2100h
Outcomes	**Mortality**: not reported **Morbidity:** not reported **Blood Pressure data**:24h BP change by 24h ABPM, data was obtained from graph and text (fig 2 on 209)

Morgan 1997 *(Continued)*

	Adverse Events: not reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not reported
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding (performance bias and detection bias) All outcomes	High risk	not used
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed, 2 patients ABPM data was eliminated
Selective reporting (reporting bias)	High risk	Morning SBP, DBP were not reported
Other bias	Unclear risk	carryover effects were not reported

Myburgh 1995

Methods	open randomized crossover trial. After 4 weeks run-in phase, patients received ramipril in the morning and at bedtime each for 4 weeks Sample size calculation: not reported carryover effects: not reported no washout period between treatment arms
Participants	Country: South African Number randomised: 39 gender: 35 men, 4 women age range: 24-73 years mean age: 49 years Ethnicity: not reported inclusion criteria: sitting DBP≥95 mm Hg and <114 mm Hg exclusion criteria: not stated
Interventions	2.5 mg od ramipril taken at 8 AM to 11AM or at 8 PM to 11PM
Outcomes	**Mortality**: not reported **Morbidity:** not reported **Blood Pressure data**:24h BP change by 24h ABPM, data was obtained from graph and text (fig 1 on page 1302 and fig 2 on page 1303) **Adverse Events:** withdrawals due to adverse events

Myburgh 1995 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not reported
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding (performance bias and detection bias) All outcomes	High risk	open label
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were reported. Three patients was excluded due to increase dose of ramipril to 5 mg, three patients withdrawn because of adverse events
Selective reporting (reporting bias)	High risk	Morning SBP, DBP were not reported
Other bias	Unclear risk	carryover effects were not reported

Neutel 2005

Methods	multicenter, double-blind, double-dummy, randomized, blinded end point, crossover study. After 4 weeks single-blind placebo run-in period, patients received chronotherapeutic propranolol and propranolol each for 4 weeks Sample size calculation: not reported carryover effects: not reported no washout period between treatment arms
Participants	Country: not reported Number randomised: 44 gender: 31 men, 13 women mean age: 53.4±8.46 years Ethnicity: Caucasian 27, African American 5, Asian 3, Hispanic 5, Other 4 inclusion criteria: seated DBP of 95–114 mm Hg and a mean daytime ambulatory DBP (8 a.m.to 4 p.m.) of 90–114 mm Hg exclusion criteria: mean DBP ≥115 mm Hg and/or a mean SBP≥200 mm Hg
Interventions	120 mg od chronotherapeutic delayed-release propranolol (Innopran XL) dosed at bedtime: N=44 120 mg od traditional propranolol (Inderal LA) dosed in the morning : N=44
Outcomes	**Mortality**: not reported **Morbidity:** not reported **Blood Pressure data**:24h BP change, morning (6 am to noon) BP change by 34h ABPM, data was obtained from text.

Neutel 2005 *(Continued)*

	Adverse Events: not reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not reported
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	double-dummy
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were reported. Three patients were excluded, one was excluded by the investigator for being uncooperative and noncompliant with study medication, one for being off study medication for a significant period of time, and one patient was removed for alcohol abuse.
Selective reporting (reporting bias)	Low risk	all outcomes were reported.
Other bias	Unclear risk	carryover effects were not reported

Nold 1998

Methods	open, randomized, crossover trial. After 1 week run-in period, each patient received two treatment period((each 3 weeks). Sample size calculation: not reported carryover effects: not reported no washout period between treatment arms
Participants	Country: Germany Number randomised: 13, 12 completed gender: 5 women, 7 men mean age: 46.9±13.8 years Ethnicity:not reported inclusion criteria: office DBP 95-115 mm Hg, 18-75 years, normal body weights exclusion criteria: malignant and secondary hypertension, history of angina pectoris, coronary heart disease, cerebrovascular event, myocardial infarction during the preceding 12 months, heart failure, arrhythmias, other severe concomitant pathological condition, child-bearing women
Interventions	5 mg od amlodipine was administered at 0800 h or at 2000h
Outcomes	**Mortality**: not reported **Morbidity:** not reported **Blood Pressure data**:24h BP change by 24h ABPM, data was obtained from fig 1 on page 21 and fig 2 on page 22

Nold 1998 *(Continued)*

	Adverse Events: not reported
Notes	supported by grants from Pfizer GmbH, Karisruhe, Germany

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not reported
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding (performance bias and detection bias) All outcomes	High risk	open
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data on all participants were reported. one patient withdrawn for missing ABPM data.
Selective reporting (reporting bias)	High risk	Morning SBP, DBP were not reported
Other bias	Unclear risk	carryover effects were not reported; sponsorship or funding of this study and conflict of interest were not declared by the authors in the article

Palatini 1992

Methods	randomized, doubled blind, crossover study. 2 weeks placebo run-in period, two treatment period (each 4 weeks) Sample size calculation: not reported carryover effects: not reported no washout period between treatment arms
Participants	Country: not reported Number randomised: 18 gender: 12 men, 6 women age: 48±7 years Ethnicity: not reported inclusion criteria: DBP 95-114mm Hg exclusion criteria: secondary hypertension, renal or hepatic diseases, heart failure, postural hypotension, myocardial infarction or cerebrovascular accident within the past 6 months, unstable angina, valvular disease
Interventions	20 mg od quinapril was administered at 8 AM and matching placebo was administered at 10pm for 4 weeks (N = 18) matching placebo was administered at 8 am and 20 mg od quinapril was administered at 10 PM for 4 weeks (N = 18)
Outcomes	**Mortality**: not reported

Palatini 1992 *(Continued)*

	Morbidity: not reported **Blood Pressure data**:24h BP change by 24h ABPM, data was obtained from fig 4 and fig 5 on page 1424 **Adverse Events:** No patient reported any side effects during the entire study period
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not reported
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	matching placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	all patients completed the study
Selective reporting (reporting bias)	High risk	Morning SBP, DBP were not reported.
Other bias	Unclear risk	carryover effects were not reported

Pechere 1998

Methods	randomized, double-blind, double-dummy, crossover design. After 2 weeks single-blind placebo period, each patient received two treatment periods (each 6 weeks) Sample size calculation: not reported carryover effects: not reported no washout period between treatment arms
Participants	Country: Switzerland Number randomised: 21, 20 completed gender: 14 men, 7 women age range: 35-70 years Ethnicity: not reported inclusion criteria: uncomplicated, mild to moderate essential hypertension, normal serum creatinine levels, office DBP range 95-115 mm Hg. exclusion criteria: not reported
Interventions	100 mg od Irbesartan taken in the morning: N=10 100 mg od Irbesartan taken on the evening: N=10 20 mg od Enalapril taken in the morning: N=10 20 mg od Enalapril taken on the evening: N=10

Pechere 1998 *(Continued)*

Outcomes	**Mortality**: not reported **Morbidity:** not reported **Blood Pressure data**:24h BP change by 24h ABPM, data was obtained from table 3 on page 390 **Adverse Events:** not reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not reported
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	capsules of the same appearance, double dummy
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were reported. One patient interrupted the study because his blood pressure increased markedly
Selective reporting (reporting bias)	High risk	Morning SBP, DBP were not reported
Other bias	Unclear risk	carryover effects were not reported

Qiu 2003

Methods	perspective, double-blind, randomized, crossover design.1- to 2-week wash-out period for patients who were currently receiving antihypertensive therapy; 2-week single-blind placebo run-in period; 12-week double-blind crossover treatment period (each 6 weeks) sample size calculation: yes carryover effects: not reported no washout period between treatment arms
Participants	Country: China Number randomised: 62, 60 completed mean age: 57.5±10.5 years gender: 44 men, 16 women Ethnicity: Chinese inclusion criteria: aged 21-77 years, 3 seated office DBP≥95 mm Hg and ≤114 mm Hg, and mean ambulatory daytime SBP≥135 mm Hg or DBP≥85 mm Hg. exclusion criteria: secondary hypertension, SBP>200 mm Hg or DBP≧ 115 mm Hg, bradycardia or tachycardial, stroke or myocardial infarction in the previous 6 months, congestive heart failure, clinically significant hepatic or renal disease, uncontrolled diabetes mellitus, life-style factors such as night-shift work, history of drug and alcohol abuse, neurologic and psychiatric illnesses, and women who were pregnant or breast-feeding.
Interventions	5 mg od amlodipine at 7AM, matching placebo at 9PM: N=62

Qiu 2003 *(Continued)*

	5 mg od amlodipine at 9 PM, matching placebo at 7AM: N=62
Outcomes	**Mortality**: not reported **Morbidity:** not reported **Blood Pressure data**:24h BP by 24h ABPM, data was obtained from fig 2 on page338 **Adverse Events:** not reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	randomization schedule
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	matching placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data on all patients were reported. Two patients withdrawn for adverse events
Selective reporting (reporting bias)	High risk	Morning SBP, DBP were not reported
Other bias	Unclear risk	carryover effects were not reported

White 1999a

Methods	randomized, double blind , double-dummy, crossover design. 3-week single blind, placebo run-in period, 8-week double-blind crossover treatment period (each 4 weeks) sample size calculation: yes carryover effects: not reported no washout period between treatment arms
Participants	Country: the United States Number randomised: 85,75 completed Mean age: 57.8±9.1(SD) years gender: 43 men, 32 women, . Ethnicity: 46 White, 26 Black, 2 Hispanic, 1 Asian. Inclusion criteria: age≥21 years, seated office DBP≥90 mm Hg and ≥109 mm Hg exclusion criteria: secondary hypertension, SBP>200 mm Hg or DBP≥110 mm Hg, bradycardia , tachycardia , stroke or myocardial infarction in the previous 6 months, congestive heart failure, clinically significant hepatic or renal disease, uncontrolled diabetes mellitus, life-style factors such as night-shift work or regular naps during the daytime, or history of allergy or intolerance to study medications.
Interventions	20 mg nisoldipine ER in the morning , and matching placebo in the evening, N=85 20 mg nisoldipine ER in the evening, and matching placebo in the morning: N=85

White 1999a *(Continued)*

Outcomes	**Mortality**: not reported **Morbidity:** not reported **Blood Pressure data**: 24h BP change by 24h ABPM (table 3 on page 809) **Adverse Events:** not reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	randomization schedule
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	double-dummy, matching placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data in all patients were reported. eight patient withdrawn for adverse events, two patients were lost to follow-up.
Selective reporting (reporting bias)	Low risk	All outcomes were reported.
Other bias	Unclear risk	carryover effects were not reported.

BP: blood pressure
SBP: Systolic blood pressure
DBP: diastolic blood pressure
MI: Myocardial infarction
GITS: gastrointestinal therapeutic system
HR: heart rate
ABPM: ambulatory blood pressure monitoring
JNC: Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
ER: extended-release
SD: standard deviation
SE: standard error
h: hour
BMI: body mass index
WHO: World Health Organization
COER: controlled onset extended release
GRD: graded-release diltiazem HCl extended-release
PROBE: prospective, randomized, open-label, blinded end point
MAPEC: Ambulatory Blood Pressure Monitoring in the Prediction of Cardiovascular Events and Effects of Chronotherapy

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

Study	Reason for exclusion
Bakris 2002	Different drugs were used in treatments arms (COER-verapamil versus (Enalapril or Losartan))

Study	Reason for exclusion
Beliaev 2002	not RCT
Beliaev 2003	not RCT
Black 2003	Different drugs were used in treatments arms (COER-verapamil versus (atenolol or HCTZ))
Calvo 2006	not monotherapy. patients were receiving 3 antihypertensive drugs in a single morning dose. Patients were randomly assigned to one of two groups according to the modification in their treatment strategy: a) Changing one of the drugs, but keeping all 3 in the morning. b) The same approach but prescribing one of the drugs to be taken at bedtime.
Carpentiere 1984	RCT, but period of treatment was 1 week and the minimum for inclusion was 3 weeks.
Conte 1998	not randomised, review article
Cooke 1994	not randomised, review article
Fogari 1988	not monotherapy
Fogari 1993	triple-way crossover design
Glasser 1999	not randomised, review article
Glasser 2000	not RCT
Greminger 1994	randomized double-blind crossover study, but period of treatment was 1 week and the minimum for inclusion is three weeks.
Gupta 1995	healthy men, not RCT
Hermida 1997	RCT, course was only one week , but the minimum for inclusion was three weeks.
Hermida 2003a	not monotherapy, HDR and ASA on awakening, or HDR and ASA at bedtime
Hermida 2005	not monotherapy, HDR and ASA on awakening, or HDR and ASA at bedtime
Hermida 2005c	not monotherapy, HDR and ASA on awakening, or HDR and ASA at bedtime
Hermida 2005d	the scheme consisting of >=3 antihypertensive drugs
Hermida 2008b	not monotherapy
Huape-Arreola 2006	not monotherapy
Kitahara 2004	the same drug, but not the same dose. cilnidipine (5 mg od) was administered at bedtime or in the morning. In one group, a morning dosing regimen of cilnidipine was started from an initial dose of 5 mg (once daily). The dose was increased until either the casual BP became optimal or a dose of 20 mg was reached; The dose at this time was continued for 8 weeks. Thereafter, a bedtime dosing regimen with the same dosage was followed for an additional 8 weeks. In the other group, bedtime dosing with cilnidipine was started from the same initial dose and increased in the same way; Thereafter the same dose was administered in the morning for an additional 8 weeks. So, for one patient in this trial, the dose was the same, but the dose wasn't the same in all patients.
Koga 2005	Patients treated first-line antihypertension drugs still had high blood pressure in the morning were given carvedilol.

Study	Reason for exclusion
Kuroda 2004	the same drug, but not the same dose. Patients taken trandolapril (1mg od) at bedtime or just after breakfast. After 4 weeks of treatment the dosage was increased to 2 mg of trandolapril unless the patient's BP had already been reduced to below 150 mmHg in systole and 90 mmHg in diastole, or side effects had occurred. Mean dose in each groups was different (morning administration group: 1.4±0.5; Bedtime administration group: 1.2±0.5), so the dose in all patients was not the same.
Lauro 1984	lack of the data. The trial showed there was no statistically difference in 24h blood pressure, but no data was reported.
Macchiarulo 1999	triple-way crossover design
Mallion 1992	No relevant endpoints. Compliance was primary outcome
Mengden 1993	outcomes of interest not reported
Neutel 1996	compared with placebo
Niegowska 2000	Not RCT
Panfilov 1988	NOT RCT
Potter 1990	337 patients were studied, but 257patients completed the study (31 were not randomised).
Shiga 1993	No relevant endpoints. Maximum plasma concentration (Cmax) and Time to maximum plasma concentration (Tmax) was primary outcome
Sica 2003	Healthy male
Sica 2004	placebo-controlled
Smith 2001a	compared with placebo
Smolensky 2007	not RCT
Sunaga 1995	The treatment period for this trial was less than two weeks
Sundberg 1991	not RCT
Tokbaeva 1996	Not RCT
Tykarski 2003	the trial has published in abstract form.
White 1995	compared with placebo
White 1997	placebo-controlled
White 1998	Different drugs in comparator arms (nifedipine GITS versus COER-verapamil)
White 1999b	This was not an original study. It analysed the data from White 1998 (Comparison of effects of controlled onset extended release verapamil at bedtime and nifedipine gastrointestinal therapeutic system on arising on early morning blood pressure, heart rate, and the heart rate-blood pressure product. Am J Cardiol 1998;81(4):424-31)
White 1999c	This was not an original study. It compares pooled data from three independent studies. These three papers were not referenced. We had written to White WB seeking a clarification, but there has been no reply.

Study	Reason for exclusion
White 1999d	This were not an original study. It compares pooled data from three independent studies. These three papers were not referenced. We had written to White WB seeking a clarification, but there has been no reply.
White 2001a	This was not an original study. It compares pooled data from three independent studies. These three papers were not referenced. We had written to White WB seeking a clarification, but there has been no reply.
White 2001b	This was not an original study. It compares pooled data from three independent studies. These three papers were not referenced. We had written to White WB seeking a clarification, but there has been no reply.
White 2002a	Different drugs in comparator arms (COER-verapamil versus (enalapril or losartan))
White 2004	Different drugs in comparator arms (diltiazem versus ramipril)
Witte 1993	No relevant endpoints. Daytime,nighttime and rhythm of blood pressure were outcome.
Wright 1976	not monotherapy, the drugs of control group administered by three times daily, and ambulatory 24 hour mean BP was not measured
Wright 1982	duration of treatment only 2 weeks
Wright 2004	Different drugs in comparator arms (diltiazem versus amlodipine)
Yan 2009	not monotherapy, lifestyle modifications and ASA on awakening, or lifestyle modifications and ASA at bedtime
Zaslavskaia 1988	not RCT
Zaslavskaia 1998a	RCT, but the treatment period for this trial was only 10 days
Zaslavskaia 1998b	RCT, but the treatment period for this trial was less than three weeks
Zaslavskaia 1999a	RCT, but the study evaluated the circadian rhythms of systolic, diastolic and mean arterial pressure, HR before and after ramipril intake throughout 24 h.
Zaslavskaia 1999b	not RCT
Zaslavskaia 2000b	RCT, but aimed at circadian study of blood pressure
Zaslavskaya 1995	not RCT
Zhou 2004	combination therapy

RCT: randomized controlled trial
HCTZ: hydrochlorothiazide
ASA: aspirin
HDR: nonpharmacological hygienic-dietary recommendations

Characteristics of studies awaiting assessment *[ordered by study ID]*

Bernard 1994

Methods

Bernard 1994 *(Continued)*

Participants	
Interventions	
Outcomes	
Notes	Awaiting article retrieval

Hermida 2003b

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting article retrieval

Meilhac 1992

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting article retrieval

Mori 2007

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting article retrieval

White 2003

Methods	

White 2003 *(Continued)*

Participants	
Interventions	
Outcomes	
Notes	Awaiting article retrieval (abstract)

Zaslavskaia 1994

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting article retrieval

Zaslavskaia 1996

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting article retrieval

DATA AND ANALYSES

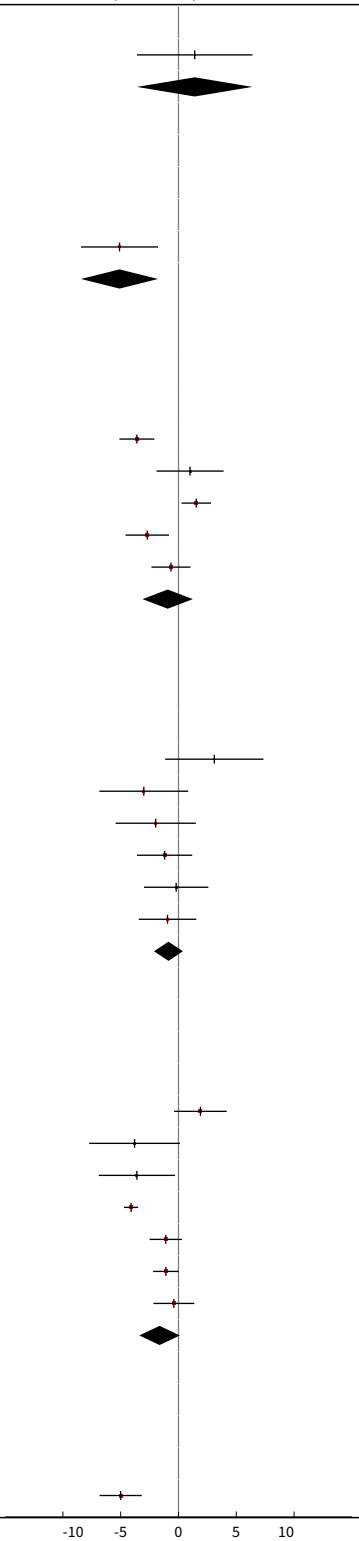
Comparison 1. evening versus morning dosing regimen

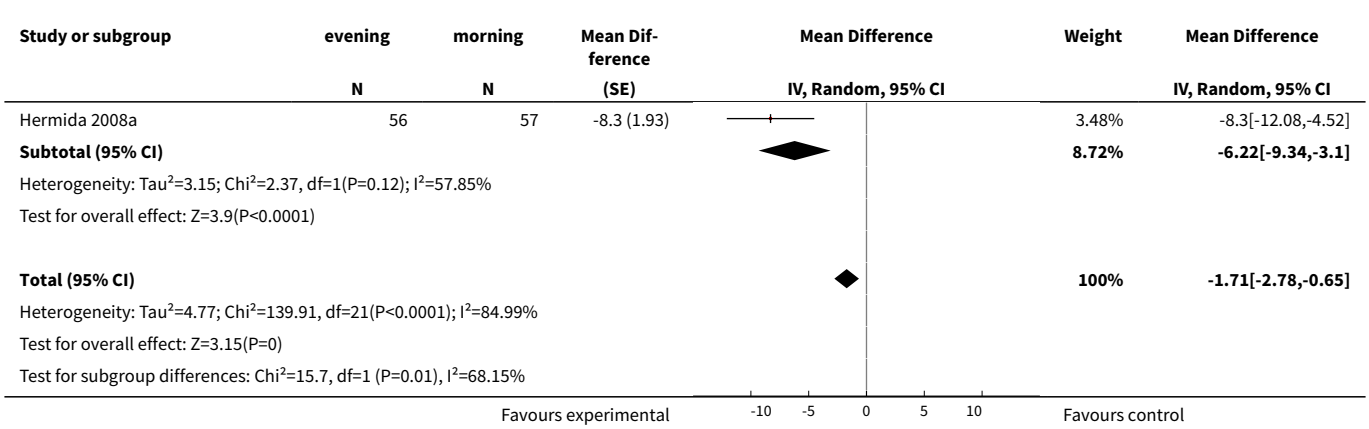
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 24 h mean systolic blood pressure	21	2152	Mean Difference (Random, 95% CI)	-1.71 [-2.78, -0.65]
1.1 β-blockers	1	82	Mean Difference (Random, 95% CI)	1.4 [-3.60, 6.40]
1.2 α-blockers	1	39	Mean Difference (Random, 95% CI)	-5.1 [-8.43, -1.77]
1.3 ACEIs	5	277	Mean Difference (Random, 95% CI)	-0.93 [-3.11, 1.24]

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.4 ARBs	6	632	Mean Difference (Random, 95% CI)	-0.87 [-2.12, 0.38]
1.5 CCBs	7	951	Mean Difference (Random, 95% CI)	-1.64 [-3.39, 0.12]
1.6 Diuretics	2	171	Mean Difference (Random, 95% CI)	-6.22 [-9.34, -3.10]
2 24 h mean diastolic blood pressure	21	2158	Std. Mean Difference (Random, 95% CI)	-1.38 [-2.13, -0.62]
2.1 β-blockers	1	88	Std. Mean Difference (Random, 95% CI)	1.1 [-2.27, 4.47]
2.2 α-blockers	1	39	Std. Mean Difference (Random, 95% CI)	-2.7 [-5.17, -0.23]
2.3 ACEIs	5	277	Std. Mean Difference (Random, 95% CI)	-1.56 [-3.18, 0.06]
2.4 ARBs	6	632	Std. Mean Difference (Random, 95% CI)	-0.72 [-1.86, 0.43]
2.5 CCBs	7	951	Std. Mean Difference (Random, 95% CI)	-0.61 [-1.58, 0.35]
2.6 Diuretics	2	171	Std. Mean Difference (Random, 95% CI)	-5.60 [-6.82, -4.38]
3 morning mean sys-tolic blood pressure	3	391	Mean Difference (Random, 95% CI)	-1.62 [-4.19, 0.95]
3.1 β-blockers	1	82	Mean Difference (Random, 95% CI)	1.5 [-2.15, 5.15]
3.2 CCBs	2	309	Mean Difference (Random, 95% CI)	-2.68 [-4.46, -0.89]
4 morning mean di-astolic blood pres-sure	3	391	Mean Difference (Random, 95% CI)	-1.21 [-3.28, 0.86]
4.1 β-blockers	1	82	Mean Difference (Random, 95% CI)	0.4 [-2.09, 2.89]
4.2 CCBs	2	309	Mean Difference (Random, 95% CI)	-1.87 [-4.32, 0.58]
5 overall adverse events	5	702	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.37, 1.65]
5.1 ACEIs	1	120	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.10, 2.63]
5.2 CCBs	2	403	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.11, 2.49]
5.3 Diuretics	2	179	Risk Ratio (M-H, Random, 95% CI)	1.66 [0.56, 4.90]
6 withdrawals due to adverse events	6	1042	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.26, 1.07]
6.1 ACEIs	1	120	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.06, 15.62]
6.2 ARBs	2	375	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.06, 1.41]
6.3 CCBs	3	547	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.26, 1.33]

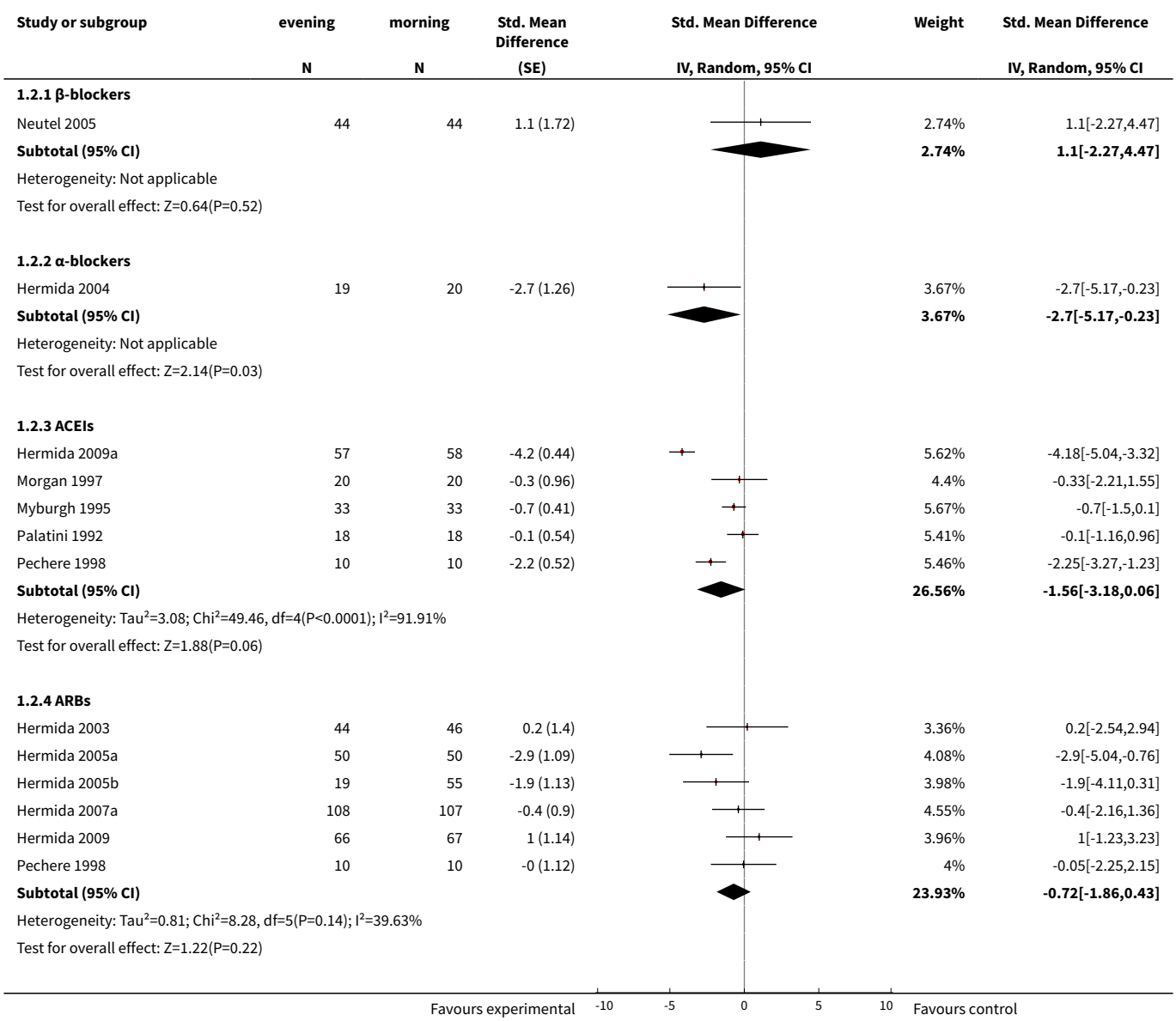
Analysis 1.1. Comparison 1 evening versus morning dosing regimen, Outcome 1 24 h mean systolic blood pressure.

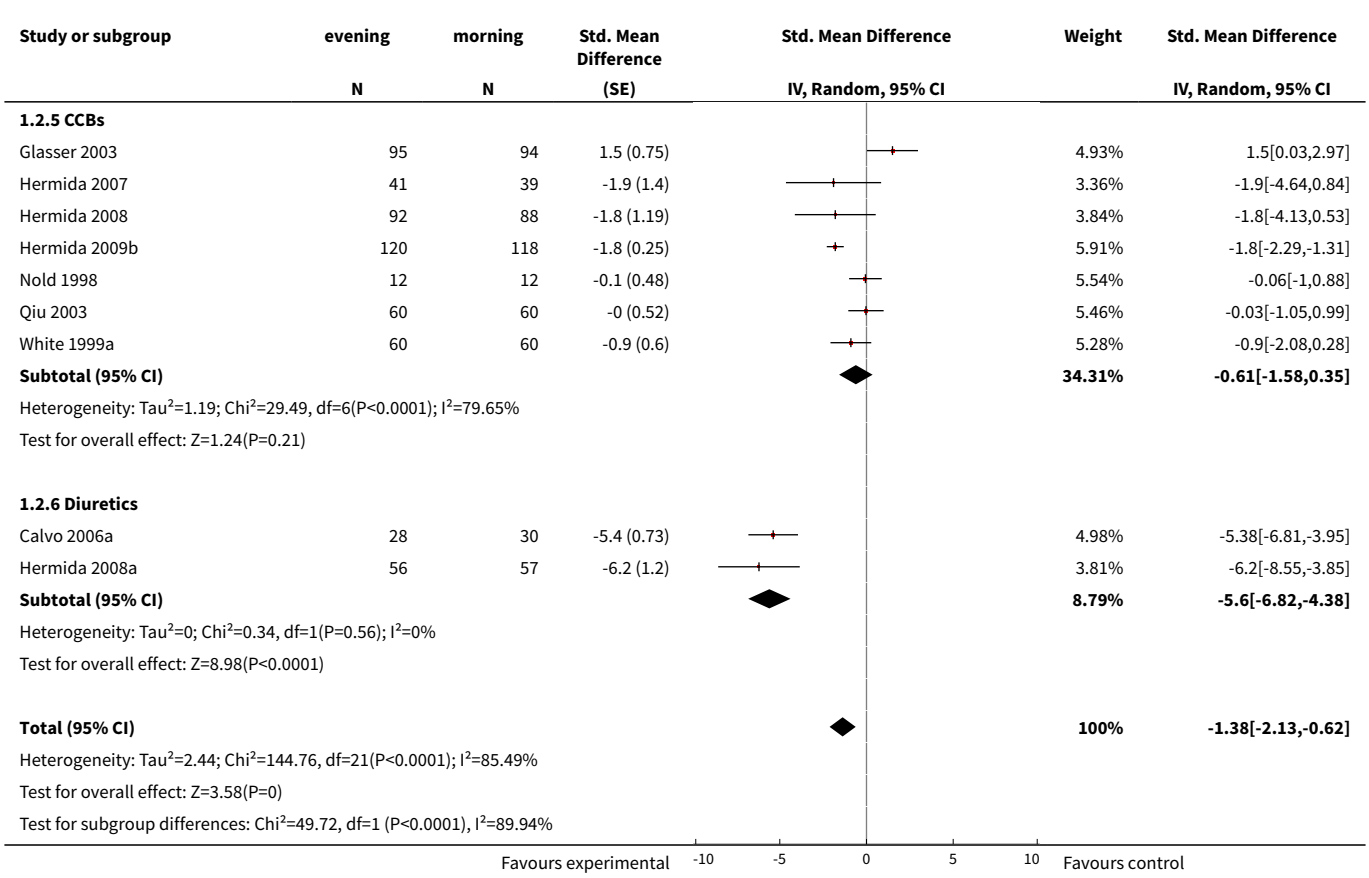
Study or subgroup	evening N	morning N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
1.1.1 β-blockers						
Neutel 2005	41	41	1.4 (2.55)		2.62%	1.4[-3.6,6.4]
Subtotal (95% CI)					**2.62%**	**1.4[-3.6,6.4]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.55(P=0.58)						
1.1.2 α-blockers						
Hermida 2004	19	20	-5.1 (1.7)		3.86%	-5.1[-8.43,-1.77]
Subtotal (95% CI)					**3.86%**	**-5.1[-8.43,-1.77]**
Heterogeneity: Not applicable						
Test for overall effect: Z=3(P=0)						
1.1.3 ACEIs						
Hermida 2009a	57	58	-3.6 (0.77)		5.51%	-3.6[-5.11,-2.09]
Morgan 1997	20	20	1 (1.48)		4.24%	1[-1.9,3.9]
Myburgh 1995	33	33	1.5 (0.65)		5.69%	1.54[0.27,2.81]
Palatini 1992	18	18	-2.7 (0.96)		5.19%	-2.7[-4.58,-0.82]
Pechere 1998	10	10	-0.6 (0.86)		5.36%	-0.65[-2.34,1.04]
Subtotal (95% CI)					**25.98%**	**-0.93[-3.11,1.24]**
Heterogeneity: Tau^2=5.24; Chi^2=31.6, df=4(P<0.0001); I^2=87.34%						
Test for overall effect: Z=0.84(P=0.4)						
1.1.4 ARBs						
Hermida 2003	44	46	3.1 (2.17)		3.12%	3.1[-1.15,7.35]
Hermida 2005a	50	50	-3 (1.96)		3.43%	-3[-6.84,0.84]
Hermida 2005b	19	55	-2 (1.77)		3.74%	-1.97[-5.44,1.5]
Hermida 2007a	108	107	-1.2 (1.22)		4.72%	-1.2[-3.59,1.19]
Hermida 2009	66	67	-0.2 (1.42)		4.35%	-0.2[-2.98,2.58]
Pechere 1998	10	10	-0.9 (1.27)		4.63%	-0.95[-3.44,1.54]
Subtotal (95% CI)					**23.98%**	**-0.87[-2.12,0.38]**
Heterogeneity: Tau^2=0.1; Chi^2=5.21, df=5(P=0.39); I^2=4.1%						
Test for overall effect: Z=1.36(P=0.17)						
1.1.5 CCBs						
Glasser 2003	95	94	1.9 (1.16)		4.83%	1.9[-0.37,4.17]
Hermida 2007	41	39	-3.8 (2)		3.37%	-3.8[-7.72,0.12]
Hermida 2008	92	88	-3.6 (1.68)		3.89%	-3.6[-6.89,-0.31]
Hermida 2009b	120	118	-4.1 (0.31)		6.07%	-4.1[-4.71,-3.49]
Nold 1998	12	12	-1.1 (0.71)		5.6%	-1.1[-2.49,0.29]
Qiu 2003	60	60	-1.1 (0.56)		5.81%	-1.09[-2.19,0.01]
White 1999a	60	60	-0.4 (0.9)		5.29%	-0.4[-2.16,1.36]
Subtotal (95% CI)					**34.85%**	**-1.64[-3.39,0.12]**
Heterogeneity: Tau^2=4.48; Chi^2=56.57, df=6(P<0.0001); I^2=89.39%						
Test for overall effect: Z=1.83(P=0.07)						
1.1.6 Diuretics						
Calvo 2006a	28	30	-5 (0.93)		5.24%	-5[-6.82,-3.18]



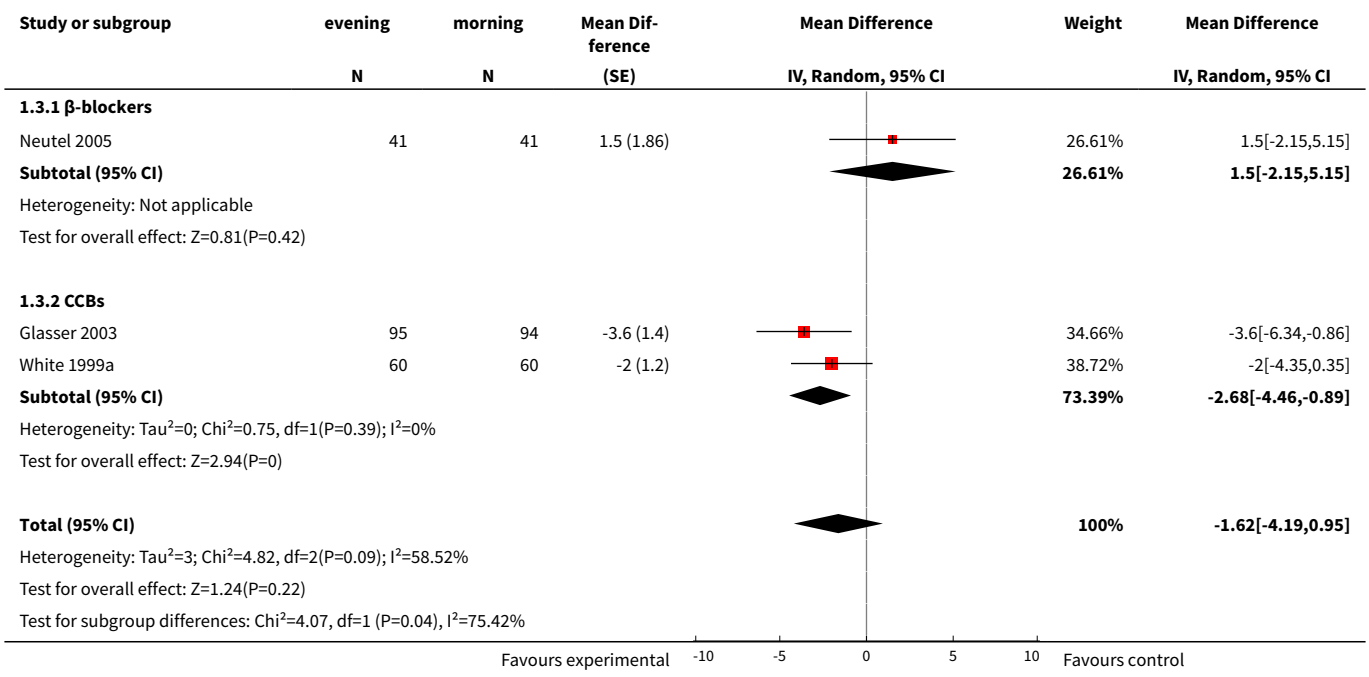


Analysis 1.2. Comparison 1 evening versus morning dosing regimen, Outcome 2 24 h mean diastolic blood pressure.



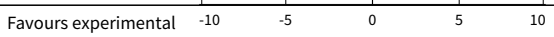


Analysis 1.3. Comparison 1 evening versus morning dosing regimen, Outcome 3 morning mean systolic blood pressure.



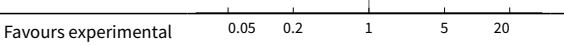
Analysis 1.4. Comparison 1 evening versus morning dosing regimen, Outcome 4 morning mean diastolic blood pressure.

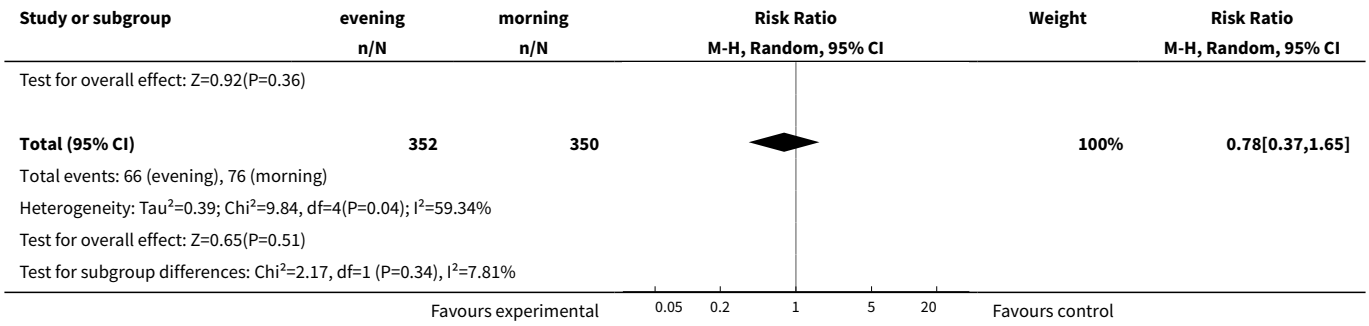
Study or subgroup	evening N	morning N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
1.4.1 β-blockers						
Neutel 2005	41	41	0.4 (1.27)		29.17%	0.4[-2.09,2.89]
Subtotal (95% CI)					**29.17%**	**0.4[-2.09,2.89]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.31(P=0.75)						
1.4.2 CCBs						
Glasser 2003	95	94	-3.1 (0.94)		36.07%	-3.1[-4.94,-1.26]
White 1999a	60	60	-0.6 (1)		34.76%	-0.6[-2.56,1.36]
Subtotal (95% CI)					**70.83%**	**-1.87[-4.32,0.58]**
Heterogeneity: Tau^2=2.18; Chi^2=3.32, df=1(P=0.07); I^2=69.86%						
Test for overall effect: Z=1.5(P=0.13)						
Total (95% CI)					**100%**	**-1.21[-3.28,0.86]**
Heterogeneity: Tau^2=2.2; Chi^2=5.92, df=2(P=0.05); I^2=66.21%						
Test for overall effect: Z=1.15(P=0.25)						
Test for subgroup differences: Chi^2=1.63, df=1 (P=0.2), I^2=38.56%						



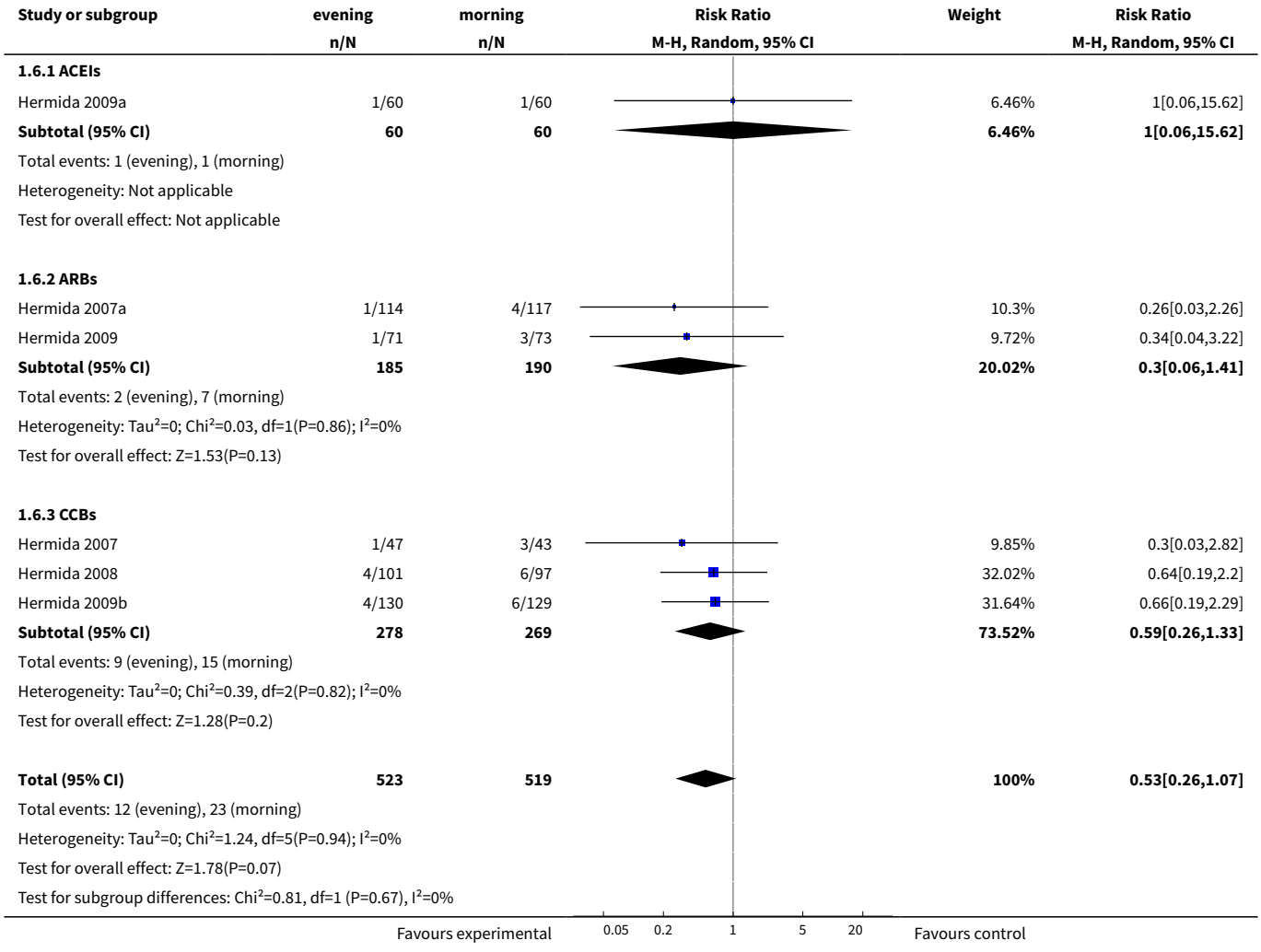
Analysis 1.5. Comparison 1 evening versus morning dosing regimen, Outcome 5 overall adverse events.

Study or subgroup	evening n/N	morning n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 ACEIs					
Hermida 2009a	2/60	4/60		13.29%	0.5[0.1,2.63]
Subtotal (95% CI)	**60**	**60**		**13.29%**	**0.5[0.1,2.63]**
Total events: 2 (evening), 4 (morning)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.82(P=0.41)					
1.5.2 CCBs					
Glasser 2003	52/103	50/102		35.71%	1.03[0.78,1.36]
Hermida 2008	4/101	17/97		21.63%	0.23[0.08,0.65]
Subtotal (95% CI)	**204**	**199**		**57.34%**	**0.52[0.11,2.49]**
Total events: 56 (evening), 67 (morning)					
Heterogeneity: Tau^2=1.13; Chi^2=8.33, df=1(P=0); I^2=87.99%					
Test for overall effect: Z=0.82(P=0.42)					
1.5.3 Diuretics					
Calvo 2006a	4/28	2/30		13.73%	2.14[0.43,10.8]
Hermida 2008a	4/60	3/61		15.64%	1.36[0.32,5.8]
Subtotal (95% CI)	**88**	**91**		**29.37%**	**1.66[0.56,4.9]**
Total events: 8 (evening), 5 (morning)					
Heterogeneity: Tau^2=0; Chi^2=0.17, df=1(P=0.68); I^2=0%					





Analysis 1.6. Comparison 1 evening versus morning dosing regimen, Outcome 6 withdrawals due to adverse events.



APPENDICES

Appendix 1. Cochrane Central Register of Controlled Trials search strategy

4th Quarter 2009

1 chronotherap$.af.
2 chronomodulat$.af.
3 chronopharm$.af.
4 1 or 2 or 3
5 hypertens$.mp.
6 exp Hypertension/
7 blood pressure.mp. or exp Blood Pressure/
8 5 or 6 or 7
9 (morning or day or am or diurnal$ or daytim$ or awak$).mp.
10 (evening or bedtim$ or night$ or nocturnal$ or pm).mp.
11 4 and 8
12 (coer or covera or codas or cardizem or innopran).mp.
13 8 and 9 and 10
14 11 or 12 or 13

Appendix 2. MEDLINE search strategy

Ovid MEDLINE(R) 1950 to Present with Daily Update

1 randomized controlled trial.pt.
2 controlled clinical trial.pt.
3 randomized.ab.
4 placebo.ab.
5 drug therapy.fs.
6 randomly.ab.
7 trial.ab.
8 groups.ab.
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10 (animals not (humans and animals)).sh.
11 9 not 10
12 Hypertension/
13 blood pressure$.mp.
14 hypertens$.mp.
15 exp blood pressure/
16 13 or 14 or 12 or 15
17 exp Chronotherapy/
18 (chronopharm$ or chronomodulat$ or chronotherap$).mp.
19 18 or 17
20 (morning or day or am or diurnal$ or daytim$ or awak$).mp.
21 (evening or bedtim$ or night$ or nocturnal$ or pm).mp.
22 21 and 20
23 16 and (19 or 22)
24 (coer or covera or codas or cardizem or innopran).mp.
25 11 and (23 or 24)

Appendix 3. EMBASE.COM search strategy

1974 to Oct 2009

#1 random* OR factorial* OR crossover* OR placebo* OR assign* OR allocat* OR volunteer* OR doubl* NEAR/5 blind* OR singl* NEAR/5 blind*
#2 'crossover procedure'/exp
#3 'double-blind procedure'/exp
#4 'randomized controlled trial'/exp
#5 'single blind procedure'/exp
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 'hypertension'/exp
#8 hypertens*

#9 'blood pressure'/exp
#10 #7 OR #8 OR #9
#11 'chronotherapy'/exp
#12 chronopharm* OR chronomodulat* OR chronotherap*
#13 morning OR day OR am OR diurnal* OR daytim* OR awak*
#14 evening OR bedtim* OR night* OR nocturnal* OR pm
#15 #13 AND #14
#16 #11 OR #12 OR #15
#17 #6 AND #10 AND #16

Appendix 4. Chinese Biomedical Literature Database (CBM) search strategy

1978 to 2009

1 分类号=R544.1/扩展/全部复分

2 主题词:高血压/全部树/全部副主题词

3 主题词:时间疗法/全部树/全部副主题词

4 主题词:时间治疗学/全部树/全部副主题词

5 缺省:时间 or 时辰 or 择时

6 缺省:(早上 or 白天 or 醒后 or 清晨) and (晚上 or 夜间 or 睡前)

7 缺省:(早晨 or 起床 or 凌晨 or 早间 or 上午) and (晚上 or 夜间 or 睡前)

8 缺省:早晚

9 #8 or #7 or #6 or #5 or #4 or #3

10 (#1 or #2) and #9

WHAT'S NEW

Date	Event	Description
23 September 2011	Amended	amended contact details and corrected appendix 4

CONTRIBUTIONS OF AUTHORS

All authors contributed work on this systematic review. Zhao Ping and Xu Ping formulated the idea for the review and developed the basis for the protocol.

Xu Ping and Zhao Ping both acted as independent reviewers and took the lead roles in searching, identifying, and assessing studies, in data abstraction and analyses, and in writing up the draft of this review. They were equivalent in this review.

Wan Chaomin and Wang Zhengrong helped with settling discrepancies in inclusion criteria or data abstraction, confirming accuracy of data, and making suggestions on writing the draft of this review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Chinese Cochrane Centre, Chinese Centre of Evidence-based Medicine, West China Hospital of Sichuan University, China.

External sources

- China Medical Board of New York (Grant number:98-680), USA.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The title was changed to better reflect the objective of the review.

The protocol did not state that randomized cross-over trials would be included. This type of trial was included in the systematic review as it was thought that properly done randomized cross-over RCTs would add to the knowledge of the effects of evening versus conventional morning dosing regimen on blood pressure profile and cardiovascular outcomes.

Li Bingyan was a co-author of the protocol but was unable to participate in the conduct of the full review, therefore his name does not appear in the list of authors.

NOTES

Medical Subject Headings (MeSH)

*Chronotherapy; Antihypertensive Agents [therapeutic use]; Blood Pressure [drug effects]; Hypertension [drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans

INDEX TERMS

Medical Subject Headings (MeSH)

Antihypertensive Agents [*administration & dosage]; Blood Pressure [physiology]; Circadian Rhythm; Drug Administration Schedule; Hypertension [*drug therapy] [physiopathology]; Randomized Controlled Trials as Topic

MeSH check words

Humans