Pharmacotherapy for mild hypertension (Review)

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TABLE OF CONTENTS

[Intervention Review]

Pharmacotherapy for mild hypertension

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ABSTRACT

Background

People with no previous cardiovascular events or cardiovascular disease represent a primary prevention population. The benefits and harms of treating mild hypertension in primary prevention patients are not known at present. This review examines the existing randomised controlled trial (RCT) evidence.

Objectives

Primary objective: To quantify the effects of antihypertensive drug therapy on mortality and morbidity in adults with mild hypertension (systolic blood pressure (BP) 140-159 mmHg and/or diastolic BP 90-99 mmHg) and without cardiovascular disease.

Search methods

We searched CENTRAL (2011, Issue 1), MEDLINE (1948 to May 2011), EMBASE (1980 to May 2011) and reference lists of articles. The Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effectiveness (DARE) were searched for previous reviews and meta-analyses of anti-hypertensive drug treatment compared to placebo or no treatment trials up until the end of 2011.

Selection criteria

RCTs of at least 1 year duration.

Data collection and analysis

The outcomes assessed were mortality, stroke, coronary heart disease (CHD), total cardiovascular events (CVS), and withdrawals due to adverse effects.

Main results

Of 11 RCTs identified 4 were included in this review, with 8,912 participants. Treatment for 4 to 5 years with antihypertensive drugs as compared to placebo did not reduce total mortality (RR 0.85, 95% CI 0.63, 1.15). In 7,080 participants treatment with antihypertensive drugs as compared to placebo did not reduce coronary heart disease (RR 1.12, 95% CI 0.80, 1.57), stroke (RR 0.51, 95% CI 0.24, 1.08), or total cardiovascular events (RR 0.97, 95% CI 0.72, 1.32). Withdrawals due to adverse effects were increased by drug therapy (RR 4.80, 95%CI 4.14, 5.57), Absolute risk increase (ARI) 9%.

Authors' conclusions

Antihypertensive drugs used in the treatment of adults (primary prevention) with mild hypertension (systolic BP 140-159 mmHg and/or diastolic BP 90-99 mmHg) have not been shown to reduce mortality or morbidity in RCTs. Treatment caused 9% of patients to discontinue treatment due to adverse effects. More RCTs are needed in this prevalent population to know whether the benefits of treatment exceed the harms.

PLAIN LANGUAGE SUMMARY

Benefits of antihypertensive drugs for mild hypertension are unclear

Individuals with mildly elevated blood pressures, but no previous cardiovascular events, make up the majority of those considered for and receiving antihypertensive therapy. The decision to treat this population has important consequences for both the patients (e.g. adverse drug effects, lifetime of drug therapy, cost of treatment, etc.) and any third party payer (e.g. high cost of drugs, physician services, laboratory tests, etc.). In this review, existing evidence comparing the health outcomes between treated and untreated individuals are summarized. Available data from the limited number of available trials and participants showed no difference between treated and untreated individuals in heart attack, stroke, and death. About 9% of patients treated with drugs discontinued treatment due to adverse effects. Therefore, the benefits and harms of antihypertensive drug therapy in this population need to be investigated by further research.

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

Antihypertensive drug therapy compared with placebo for mild hypertension

Patient or population: Adults with mild hypertension and no cardiovascular disease
Settings: ambulatory
Intervention: Stepped care antihypertensive drug therapy
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Antihypertensive drugs				
Mortality **4 to 5 years**	**Low risk population**		**RR 0.85** (0.63 to 1.15)	8912 (4)	⊕◯◯◯ **very low**	More RCTs needed as a significant benefit may have been missed
	15 per 1000	**13 per 1000** (9 to 17)				
	High risk population					
	30 per 1000	**26 per 1000** (18 to 34)				
Total CV events 5 years	**Low risk population**		**RR 0.97** (0.72 to 1.32)	7080 (3)	⊕◯◯◯ **very low**	More RCTs needed as wide confidence intervals are consistent with a significant benefit or a significant harm
	15 per 1000	**15 per 1000** (11 to 20)				
	High risk population					
	30 per 1000	**29 per 1000** (22 to 40)				

Withdrawals due to adverse effects 5 years	**Low risk population**		**RR 4.80** (4.14 to 5.57)	17,354 (1)	⊕⊕⊕○ **moderate**	Withdrawals due to adverse effects are increased. It was downgraded to moderate as it was not limited to a primary prevention population with mild hypertension
	15 per 1000	**72 per 1000** (62 to 84)				
	High risk population					
	30 per 1000	**144 per 1000** (124 to 168)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

The median control group risk was derived from the event rate in the control group i.e. 20 per 1000 mortality, 24 per 1000 total CV events and 23 per 1000 withdrawals due to adverse effects.

BACKGROUND

Previous meta-analyses have concluded that cardiovascular events and overall mortality are decreased with antihypertensive drug therapy as compared to placebo or no treatment (Collins 1990, Gueyffier 1996, Psaty 1997, Wright 1999, Quan 2000, Psaty 2003, Wright 2009). These meta-analyses have combined subjects with mild elevations of blood pressure (stage 1), 140-159/ 90-99 mmHg, and moderate to severe elevations of blood pressure (> 160/100 mmHg). These meta-analyses have also combined patients who have had a previous cardiovascular event (secondary prevention) with subjects who have not had a cardiovascular event (primary prevention). It is commonly assumed that the treatment effect expressed as relative risk is the same for primary prevention and secondary prevention populations; however, this is not proven. Furthermore, it is expected that the absolute risk reduction would be larger in secondary prevention populations than in primary prevention populations.

At the present time, individuals with mild elevations of blood pressure and no cardiovascular disease (primary prevention) are commonly treated with antihypertensive drugs despite there being no direct evidence supporting this practice. Furthermore this represents about half of the people presently being treated with antihypertensive drugs since the proportion of patients with mild elevations in blood pressure is about the same as the proportion with moderate to severe elevations in blood pressure (Marchant 2011). Therefore it is evident that there is a need to determine whether there is a proven reduction in mortality and morbidity with antihypertensive treatment in this patient group and if so the magnitude of that reduction. An attempt to do this by limiting to trials where patients were categorized as mild hypertension has been done (Therapeutics Initiative 2007), however in that analysis the average blood pressure at baseline was 160/98 mmHg, making it clear that even in that attempt about half of the individuals had moderate elevations of blood pressure at baseline. In that analysis antihypertensive treatment reduced total cardiovascular events, but not mortality. However, the findings of that analysis cannot be assumed to be extrapolated to the patients (about half of the total) that had mild elevations of blood pressure at baseline. The objective of this review was to assess the mortality and morbidity outcomes in randomized controlled trials using individual patient data whenever possible and limit the analysis to a primary prevention population with mild elevations of blood pressure at baseline.

OBJECTIVES

1. To quantify the effects of antihypertensive drug therapy as compared to no treatment on mortality and morbidity in healthy adults with mild elevations of blood pressure (systolic BP 140-159 mmHg and/or diastolic BP 90-99 mmHg).

2. To quantify withdrawals due to adverse drug effects for antihypertensive drug therapy in healthy adults with mild hypertension.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials of at least 1 year duration.

Types of participants

A primary prevention population of men and non-pregnant women, greater than 18 years of age with mild hypertension defined as a systolic blood pressure of 140 - 159 mmHg or diastolic blood pressure 90 - 99 mmHg and no evidence of cardiovascular disease at baseline: specifically defined as no myocardial infarction (MI), angina pectoris, coronary bypass surgery, coronary angioplasty, stroke, transient ischaemic attack, carotid endarterectomy, surgery for peripheral vascular disease, intermittent claudication, or renal failure (creatinine > 1.5 times the upper limit of normal). More than 80% of patients in a trial had to have mild hypertension as defined above for the trial to be included unless individual patient data was available allowing specific inclusion of this population as defined.

Types of interventions

Treatment with an antihypertensive drug either as monotherapy or with the addition of other drugs in a stepped care approach. Control: placebo or no antihypertensive treatment.

Types of outcome measures

Primary outcomes

Total mortality
Total cardiovascular events (total stroke, total MI and total congestive heart failure CHF)

Secondary outcomes

Total stroke (fatal and nonfatal strokes)
Total coronary heart disease (fatal and non-fatal myocardial infarction, sudden death)
Withdrawals due to adverse drug effects

Search methods for identification of studies

The Database of Abstracts of Reviews of Effectiveness (DARE) and the Cochrane Database of Systematic Reviews were searched to the end of 2011 for related reviews and meta-analyses of antihypertensive drug treatment compared to placebo or no treatment

trials. Reports of relevant trials referred to in these reviews were obtained.

The following electronic databases were searched for primary studies: CENTRAL (2011, Issue 1), MEDLINE (1948 to May 2011), EMBASE (1980 to May 2011) and reference lists of articles.

Electronic databases were searched using a strategy combining the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision) with selected MeSH terms and free text terms relating to hypertension. No language restrictions were used. The MEDLINE search strategy (Appendix 1) was translated into EMBASE (Appendix 2), and CENTRAL (Appendix 3) using the appropriate controlled vocabulary as applicable.

Other sources:

a) Reference lists of all papers and relevant reviews identified

b) Authors of relevant papers were contacted regarding any further published or unpublished work

c) Authors of trials reporting incomplete information were contacted to provide the missing information

Data collection and analysis

All abstracts of trials identified by electronic searching or bibliographic scanning were screened. Those studies which appeared to meet the predetermined inclusion criteria stated above were selected on the basis of full text screening. When some trials also included subjects different than those of interest e.g.. secondary prevention, stage 2 hypertension, we attempted to get the data on the subjects with mild hypertension as defined in this review. Such information was available for a large number of subjects in the INDANA database primarily from the Australian trial (ANBP) in mild hypertension and the MRC trial in mild hypertension. Despite all efforts individual subject data were not available for the Oslo study, the USPHSHC study, and the VA-NHLBI study.

Data abstraction was undertaken by 2 independent reviewers who collected information on the following characteristics for each trial: type and dose of antihypertensive drugs used; other interventions used; patient characteristics, including co-morbid conditions; morbidity and mortality outcomes; and length of trial follow-up.

Risk of bias was also assessed independently by 2 reviewers using the risk of bias tool and the following criteria: sequence generation, allocation concealment, blinding, Incomplete outcome data, selective reporting or other biases. Disagreements between independent reviewers arising in any of the stages above were resolved by a third reviewer (JMW).

Using the Cochrane software (RevMan) a quantitative analysis was carried out based on the availability of outcome data in the defined population. Individual patient data from 3 trials (ANBP; MRC; SHEP) and all data from 1 trial (VA-NHLBI) were pooled. Meta-analysis was performed using the Mantel-Haenszel statistical method and a fixed effects model. The risk ratio of each outcome comparing treatment versus no treatment or placebo was calculated.

RESULTS

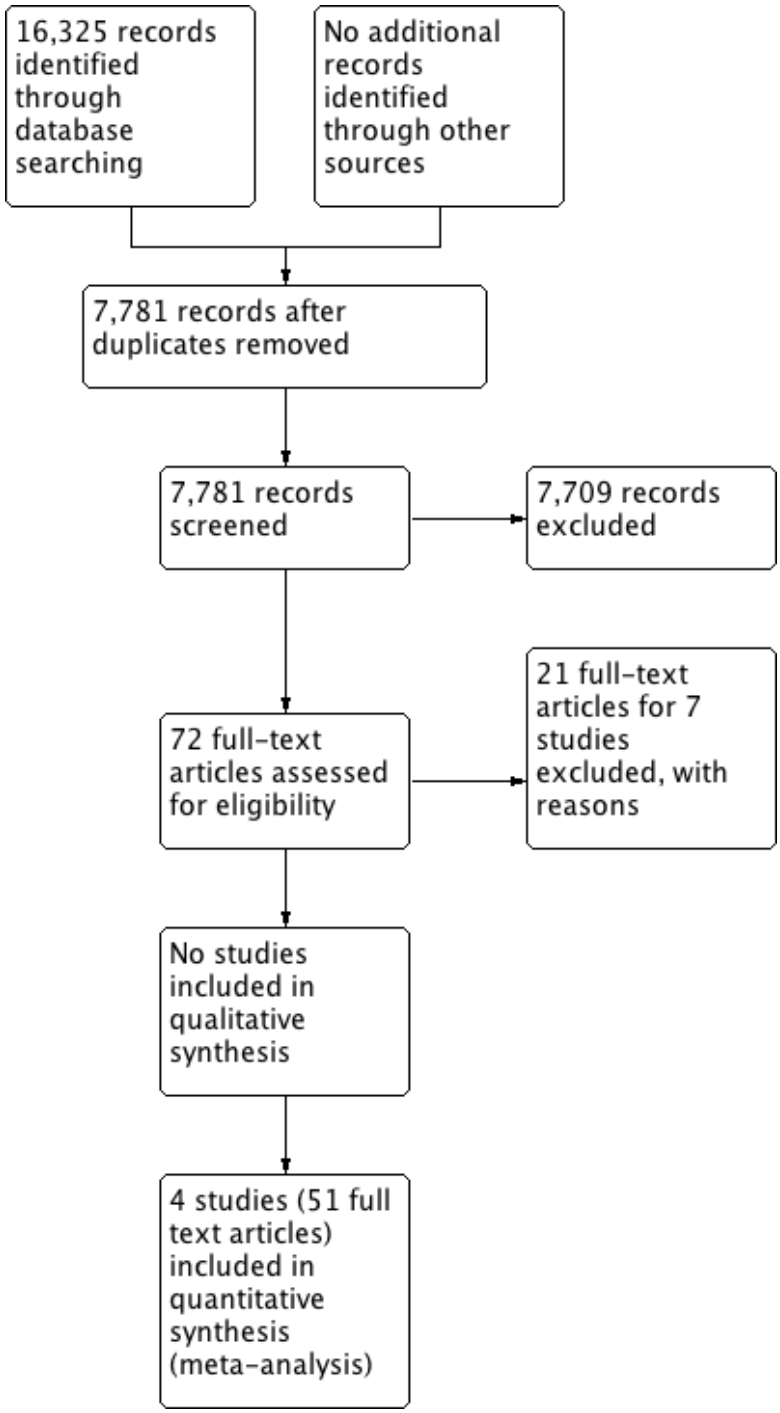
Description of studies

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

See Characteristics of included studies; Characteristics of excluded studies.

We retrieved 11 studies where antihypertensive therapy was administered for primary prevention in subjects with mild hypertension, published between 1966 and 2005 (see Figure 1). We excluded 2 trials because they had 2 or fewer subjects who met the criteria outlined in this review (MRC2, COOPE) and 3 trials because they did not have a placebo or no-treatment study group (HDFP, MRFIT, FEVER 2005). Despite considerable effort we were unable to obtain individual subject data for the Oslo, USPHSHC, and VA-NHLBI studies (2,186 patients). Based on the baseline blood pressure and standard deviation, we established that more than 20% of the patients in the Oslo Study and the USPHSHC study had moderately elevated blood pressure. Therefore these trials were excluded as they could not be expected to reflect the effects in a primary prevention population with mild hypertension. In the VA-NHLBI trial, less than 20% of subjects had moderately elevated blood pressure so we included this trial (1,012 patients). Individual subject data was obtained for ANBP, MRC, and SHEP trials and only those subjects who met the above stated criteria at baseline were included in this review (7,900 patients).The characteristics of these 4 included trials (8912 participants) in this review are summarized in the table Characteristics of included studies.

Figure 1. Study flow diagram.



Risk of bias in included studies

Risk of bias from 5 domains was assessed for each of the included studies (see Risk of bias in included studies).

Effects of interventions

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

For the 8912 participants included in this review, treatment with antihypertensive drugs as compared to no treatment did not reduce total mortality (RR 0.85, 95% CI 0.63, 1.15). Furthermore, antihypertensive treatment did not significantly reduce total stroke (RR 0.51, 95% CI 0.24, 1.08), total coronary heart disease (RR 1.12, 95% CI 0.80, 1.57) or total cardiovascular events (RR 0.97, 95% CI 0.72, 1.32) (see Data and analyses).

Withdrawals due to adverse effects (WDAEs) was only available from all patients in the MRC trials and not from the subgroup of patients with mild hypertension. Assuming that withdrawals due to adverse effects would be similar in the participants with mild hypertension and those with moderate to severe hypertension, we have calculated this value for the whole trial. This showed an increase in WDAEs with antihypertensive treatment RR 4.80 [4.14, 5.17], ARR 8.9%. The VA-NHLBI trial reported any adverse symptom 1642/508 in the treatment group and 920/504 in the no treatment group. Chemical abnormalities such as hypokalaemia were also increased in the treatment group, 216 versus the control group, 15.

DISCUSSION

Summary of main results

This review demonstrates that antihypertensive drugs used in the treatment of patients without a previous cardiovascular event (primary prevention) with mild hypertension (systolic BP 140-159 mmHg and / or diastolic BP 90-99 mmHg) have not been proven to significantly reduce any outcome including total mortality, total cardiovascular events, coronary heart disease, or stroke. This review provides data on >8,000 people followed for 5 years and suggests little or no reduction in total cardiovascular events, RR 0.97 [0.72, 1.32] (see Summary of findings for the main comparison). The review also shows a non-significant reduction in stroke, RR 0.51 [0.24, 1.08] and mortality 0.85 [0.63, 1.15] consistent with there being a real benefit of treatment, but that it wasn't demonstrable due to the paucity of events and people. Thus it remains possible, but highly unlikely, that there is an overall significant benefit of treating this group of patients with currently used medications.

However, even if the assumption is made, as is commonly done, that the relative benefits for a primary prevention population with mild hypertension are the same as for patients with moderate to severe hypertension, mortality RR 0.9 and total CV events RR 0.7 from the review of first-line treatments of hypertension (Wright 2009) then the absolute benefits would be very small. We have made this estimate from the placebo group in the largest trial in this review (MRC). The estimated absolute risk reduction in this best case scenario is 0.25% for mortality and 0.78% for total cardiovascular events over a 5 year period. This means that 400 people would have to be treated for 5 years to prevent 1 death and 128 people would have to be treated for 5 years to prevent 1 cardiovascular event. It is likely that many such patients given this information would choose non drug treatments for hypertension (e.g. diet, exercise, stress management, etc.) rather than drug therapy. They would be even less likely to choose drug treatment when they were told that these estimated benefits are a best case scenario and uncertain based on the best available evidence at this time from this review. Furthermore they must also be told that they have a 9% chance of having an adverse effect that would require them to withdraw from therapy. Withdrawals may not be that high in practice today as lower doses of thiazides and beta-blockers are used today than was used in the MRC trial.

Overall completeness and applicability of evidence

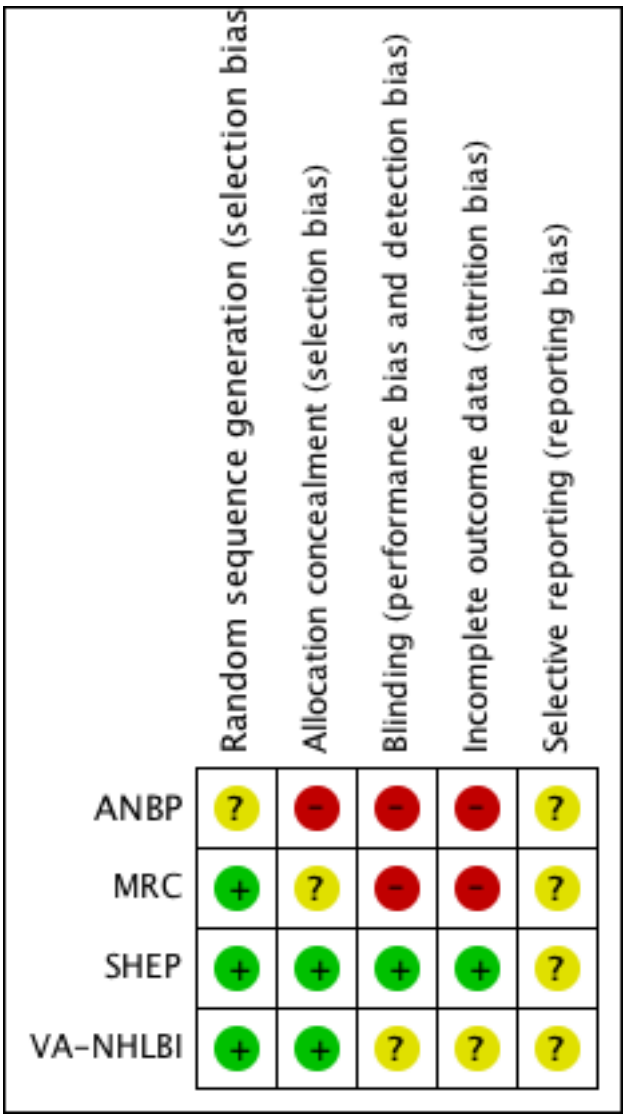
The findings of this review are limited by the inability to get individual patient data from all the trials with patients in this subgroup. The number of patients in this review in comparison to the total number of patients in the trials in shown in Table 1. However, even if we had all the data there is a good chance the findings would remain uncertain and inconclusive. This is due to the fact that patients with mild hypertension have a relatively low risk of experiencing an adverse cardiovascular event in keeping with the low number of events that were seen in this review. A 5 year study with 15,000 patients would be required to demonstrate a reduction of 30% in total cardiovascular events and of 45,000 patients to demonstrate a mortality reduction of 10%. Planned subgroup analyses were not conducted due to the paucity of outcomes in the overall data.

Quality of the evidence

The trials contributing to this review were funded by granting agencies. Nevertheless the risk of bias assessment suggests that there is a moderate to high risk of bias (Figure 2) making the magnitude of the non-significant relative risk reduction more likely to be an overestimate than an underestimate. In particular the Australian

trial (ANBP) had a high risk of ascertainment bias. As a result this trial only contributed to mortality data. The RR estimate of effect on mortality with treatment was unaffected by deselecting this trial. Another limitation is that most of the outcome data comes from the MRC trial, which we judged to have a high risk of detection bias and attrition bias. Despite the lack of financial bias in this trial the investigators were more likely to be biased in favour of treatment than against, justifying why the non-significant benefits are likely to be an overestimate.

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



Potential biases in the review process

It is unlikely that any large unpublished negative trials have been missed. It is over 20 years now since it has been accepted by the medical community that patients with mild hypertension should be treated. Therefore it is highly unlikely that trials have been conducted in this population in the last 20 years. The inability to obtain individual patient data in all relevant trials could have biased the findings.

Agreements and disagreements with other studies or reviews

As far as we are aware there have been no previous systematic reviews conducted to answer this question. The findings of this review are however in disagreement with hypertension guideline recommendations in the US, Canada and Europe. These guideline groups have recommended treatment of all adults with a blood pressure > 140/90 mmHg. The European Guidelines specify that the recommendation for pharmacologic treatment in "mild uncomplicated hypertension" is based on the outcomes of these 5 trials (ANBP; MRC; FEVER 2005; HDFP; Oslo). They do note that the evidence in favour of this recommendation is scant because older trials of "mild hypertension" treated patients whose blood pressure could be higher than grade 1 hypertension or included secondary prevention patients (Mancia 2009). We have excluded the latter 3 RCTs, FEVER 2005, HDFP and Oslo, because they had >20% of patients with moderate or higher blood pressure and FEVER 2005 plus HDFP did not have an appropriate control group. The American Society of Hypertension guidelines refers to the European Guidelines to justify this treatment threshold recommendation. The Canadian guidelines are not explicit as to how they come to their recommendations.

AUTHORS' CONCLUSIONS

Implications for practice

Since a large proportion of people treated with antihypertensive therapy are individuals with no previous cardiovascular disease (primary prevention) and mild elevations of blood pressure, the findings of this review have important implications. Most physicians have been treating such patients with false confidence that it was based on RCT evidence. Based on the best available evidence at the present time, this review does not show any significant benefit of antihypertensive drug therapy in reducing mortality, heart attacks, strokes, or overall cardiovascular events. Furthermore drug treatment caused 9% of patients to withdraw due to adverse effects. It is likely that given this evidence many individuals with no cardiovascular disease and mild hypertension would choose non-drug treatments (diet, exercise, stress management, etc.) rather than drug therapy.

Implications for research

Evidence based treatment of mild hypertension represents a challenge to the medical and research community. Hypertension, the commonest clinical condition being treated today is being treated with an assumption that it has been established that the benefits of treatment outweigh the harms, when that is not in fact the case for people with no cardiovascular disease (primary prevention) and mild hypertension. In the absence of evidence, it is entirely ethical to conduct a large RCT in primary prevention patients with mild hypertension comparing antihypertensive therapy with placebo. At the present time equipoise exists between the treated and the placebo group. In such an RCT it would be possible to compare the relative and absolute benefits and harms in people at baseline in the higher range 150-159/95-99 mmHg and in the lower range 140-149/90-94 mmHg. By following such an approach we may finally properly define hypertension as "that BP above which the benefits of treatment outweigh the harms".

ACKNOWLEDGEMENTS

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REFERENCES

References to studies included in this review

ANBP ***{published data only}***

Abernethy JD. The Australian Therapeutic Trial in Mild Hypertension. *Hypertension 1984;6(5):774-6* 1984;**6**(5): 774–776.

Abernethy JD. The need to treat mild hypertension. Misinterpretation of results from the Australian trial. *JAMA* 1986;**256**(22):3134–37.

* Anonymous. The Australian Therapeutic Trial in Mild Hypertension. Report by the management committee. *Lancet* 1980;**1**:1261–1267.

A report by the Management Committee of the Australian Theraputic Trial in Mild Hypertension. Untreated mild hypertension. *Lancet* 1982;**1**(8265):185–91.

Doyle AE. Cardiovascular morbidity and mortality in mild hypertension: The Australian Trial. *Journal of*

Cardiovascular Pharmacology 1985;**7**(Suppl 2):S10–13.
Doyle AE. The Australian Therapeutic Trial in Mild Hypertension. *Nephron* 1987;**47**(Suppl 1):115–19.
National Heart Foundation of Australia. Treatment of mild hypertension in the elderly. *Med J Aust* 1981;**2**:398–402.
Parry CA. Australian Therapeutic Trial in Mild Hypertension. [Letter]. *Lancet* 1980;**2**(8191):425.
Reader R. Australian Therapeutic Trial in Mild Hypertension. *Medical Journal of Australia* 1984;**140**(13): 752–54.
Report by Management committee of the ATTMH. Initial results of the Australian Therapeutic Trial in mild hypertension (ATTMH). *Clinical Science* 1979;**57**: 449s–452s.

MRC ***{published data only}***

Anonymous. Adverse reactions to bendrofluazide and propanolol for the treatment of mild hypertension. Report of Medical Research Council Working Party on Mild to Moderate Hypertension. *Lancet* 1981;**2**(8246):539–43.
Anonymous. Coronary heart disease in Medical Research Council trial of mild hypertension. Medical Research Council Working Party on Mild Hypertension. *British Heart Journal* 1988;**59**(3):364–378.
Anonymous. Course of blood pressure in mild hypertension after withdrawal of long term antihypertensive treatment. Medical Research Council Working Party on Mild Hypertension. *Brit Med J* 1986;**293**(6553):988–92.
Anonymous. Randomised controlled trial of treatment of mild hypertension: design and pilot trial. Report of the Medical Research Council Working party on mild to Moderate Hypertension. *Brit Med J* 1977;**1**(6074): 1437–40.
Anonymous. Stroke and coronary heart disease in mild hypertension: risk factors and the value of treatment. Medical Research Council Working Party on Mild Hypertension. *Brit Med J* 1988;**296**(6636):1565–70.
* Medical Research council Working Party. MRC trial of treatment of mild hypertension: principal results. *Br Med J* 1985;**291**:97–104.
Miall WE. Brennan PJ, Mann AH. Medical research Council's Treatment Trial for mild hypertension: an interim report. *Clinical Science and Molecular Medicine* 1976;**51**: 563s–565s.
Peart S. Results of the MRC (UK) trial of drug therapy for mild hypertension. *Clinical and Investigative Medicine* 1987;**10**(6):616–20.
Peart S. Barnes GR. Briughton PMG. Dollery CT, et al.Comparison of the antihypertensive efficacy and adverse reactions to two doses of bendrofluazide and hydrochlorothiazide and the effect of potassium supplementation on the hypotensive action of bendrofluazide: substudies of the Medical Research Council's trials of treatment of hypertension. *Journal of Clinical Pharmacology* 1987;**27**(4):271–77.

SHEP ***{published data only}***

Applegate WB. Davis BR. Black HR, et al.Prevalence of postural hypotension at baseline in the systolic hypertension in the elderly program (SHEP) cohort. *Journal of American Geriatric Society* 1991;**39**:1057–64.
Bearden D. Allman R. McDonald R, et al.Age, race, and gender variation in the utilization of coronary artery bypass surgery and angioplasty in SHEP. *Journal of the American Geriatric Society* 1994;**42**:1143–49.
Black HR. Unger D. Burlando A, et al.Part 6: Baseline physical examination findings.. *Hypertension 1991;17(3 (Suppl II)):II-77-II-101.* 1991;**17**(Suppl II):77–101.
Borhani NO. Applegate WB. Cutler JA, et al.Part 1: rationale and design. *Hypertension* 1991;**17**(Suppl II):2–15.
Brittain E. Palensky J. Blood J and Wittes J. Blinded subjective rankings as a method of assessing treatment effect: a large sample example from the systolic hypertension in the elderly program (SHEP). *Statistics in Medicine* 1997;**16**: 681–93.
Curb JD. Lee M. Jensen J, Applegate W. Part 4: baseline medical history findings. *Hypertension* 1991;**17**(Suppl II): 35–61.
Curb JD. Pressel SL. Cutler JA, et al.Effect of diuretic based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. *JAMA* 1996;**276**:1886–92.
Davis BR. Wittes J. Pressel S, et al.Statistical considerations in monitoring the systolic hypertension in the elderly program (SHEP). *Controlled Clinical Trials* 1993;**14**: 350–61.
Franse LV. Pahor M. Di Bari M, et al.Serum uric acid, diuretic treatment and risk of cardiovascular events in the systolic hypertension in the elderly program. *Journal of Hypertension* 2000;**18**:1149–54.
Frost PH. Davis BR. Burlando AJ, et al.Serum lipids and incidence of coronary heart disease. Findings from the systolic hypertension in the elderly program. *Circulation* 1996;**94**:2381–88.
Hall WD. Davis BR. Frost P, et al.Part 7: Baseline laboratory characteristics. *Hypertension* 1991;**17**(Suppl II):102–122.
Hawkins CM. Isolated systolic hypertension, morbidity and mortality: The SHEP experience. *American Journal of Geriatric Cardiology* 1993;**2**(5):25–27.
Kostis JB. Allen R. Berkson DM, et al.Correlates of ventricular ectopic activity in isolated systolic hypertension. *American Heart Journal* 1994;**127**:112–21.
Kostis JB. Davis BR. Cutler J, et al.Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. *JAMA* 1997;**278**(3): 212–216.
Kostis JB. Lacy CR. Hall D, et al.The effect of chlorthalidone on ventricular ectopic activity in patients with isolated systolic hypertension. *American Journal of Cardiology* 1994;**74**:464–67.
Kostis JB. Prineas R. Curb JD, et al.Part 8: Electrocardiographic characteristics.. *Hypertension* 1991;**17** (Suppl II):123–151.
Menard J. Day M. Chatellier G, Laragh JH. Some lessons from systolic hypertension in the elderly program (SHEP).

American Journal of Hypertension 1992;**5**:325–30.
Newman AB. Tyrrell KS, Kuller LH. Mortality over four years in SHEP participants with a low ankle-arm index. *Journal of American Geriatric Society* 1997;**45**:1472–78.
Perry HM. Davis BR. Price TR, et al.Effect of treating isolated systolic hypertension on the risk of developing various types and subtypes of stroke. *JAMA* 2000;**284**(4): 465–471.
Petrovich H. Byington R. Bailey G, et al.Part 2: screening and recruitment. *Hypertension* 1991;**17**(Suppl II):17–23.
Probstfield JL. Applegate WB. Borhani NO, et al.The systolic hypertension in the elderly program (SHEP): an intervention trial on isolated systolic hypertension. *Clinc and Exper Hypertension-Theory and Practice* 1989;**A11**(5 & 6):973–89.
Savage PJ. Pressel SL. Curb D, et al.Influence of long-term, low-dose, diuretic-based, antihypertensive therapy on glucose, lipid, uric acid, and potassium levels in older men and women with isolated systolic hypertension. *Archives of Internal Medicine 1998;158:741-751.* 1998;**158**:741–751.
SHEP cooperative research group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the SHEP. *ACP Journal Club* 1991;**115**(3):65.
* SHEP cooperative research group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991; **265**(24):3255–64. [PUBMED: 2046107]
SHEP cooperative Research Group. Rationale and design of a randomized clinical trial on prevention of stroke in isolated systolic hypertension. *Journal of Clinical Epidemiology* 1988; **41**(12):1197–1208.
Vogt TM. Schron E. Pressel S, et al.Part 3: Sociodemographic characteristics. *Hypertension* 1991;**17**(Suppl II):24–34.
Wassertheil S. Applegate WB. Berge K, et al.Change in depression as a precursor of cardiovascular events. *Archives of Internal Medicine* 1996;**156**:553–561.
Wasserthell-Smoller S. FannC. Allman RM, et al.Relation of low body mass to death and stroke in the systolic hypertension in the elderly program. *Archives of Internal Medicine* 2000;**160**:494–500.
Weiler PG. Camel GH. Chiappini M, et al.Part 9: Behavorial characteristics. *Hypertension* 1991;**17**(Suppl II): 152–161.
Wittes J. Davis B. Berge K, et al.Part 10: Analysis. *Hypertension* 1991;**17**(Suppl II):162–167.

VA-NHLBI ***{published data only}***

* Perry HM Jr, Goldman AI, Lavin MA, Schnaper HW, Fitz AE, et al.Evaluation of drug treatment in mild hypertension: VA-NHLBI feasibility trial. Plan and preliminary results of a two-year feasibility trial for a multicenter intervention study to evaluate the benefits versus the disadvantages of treating mild hypertension. *Ann N Y Acad Sci* 1978;**304**: 267–92. [PUBMED: 360921]
Perry Jr HM, et al.Treatment of mild hypertension. Preliminary results of a two year feasibility trial. *Circ Res* 1977;**40**(suppl):1180–87.

References to studies excluded from this review

COOPE ***{published data only}***

Coope J, Warrender TS. Randomised trial of treatment of hypertension in elderly patients in primary care. *BMJ* 1986; **293**:1145–51.

FEVER 2005 ***{published data only}***

* Liu L, Zhang Y, Liu G, Li W, Zhang X, Zanchetti A. The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients. *Journal of Hypertension* 2005;**23**:2157–2172.

HDFP ***{published data only}***

HDFP. Effect of stepped care treatment on the incidence of myocardial infarction and angina pectoris. 5-year findings of the hypertension detection and follow-up program. *Hypertension* 1984;**6**(Suppl 1):198–206.
HDFP. Five-year findings of the hypertension detection and follow-up program III. Reduction in stroke incidence among persons with high blood pressure. *JAMA* 1982;**247**: 633–638.
HDFP. The effect of treatment on mortality in "mild"hypertension Results of the hypertension detection and follow-up program. *N Engl J Med* 1982;**307**:976–980.
Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the Hypertension Detection and Follow-up Program: I.Reduction in mortality of persons with high blood pressure, including mild hypertension. *JAMA* 1979;**242**:2562–71.
Hypertension Detection and Follow-up Program Cooperative Group (HDFP). Five-year findings of the hypertension detection and follow-up program II Mortality by race-sex and age. *JAMA* 1979;**247**:2572–2576..

MRC2 ***{published data only}***

Medical Research Council Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. *BMJ* 1992;**304**:405–12.

MRFIT ***{published data only}***

Multiple Risk Factor Intervention Trial Research Group. Multiple risk factor intervention trial. Risk factor changes and mortality results. *JAMA* 1982 Sep 24;**248**(12): 1465–77.

Oslo ***{published data only}***

Helgeland A. Treatment of mild hypertension: a five year controlled drug trial. The Oslo study. *Am J Med* 1980 Nov; **69**(5):725–32. [PUBMED: 7001898]
Helgeland A, Leren P. Oslo study: Treatment of mild hypertension. *Nephron* 1987;**47**(Suppl 1):108–110.
Helgeland A. Baksaas IA, Leren P. Mild hypertension - early drug treatment or follow-up only? the Oslo study. *Acta Medica Scandinavica. Supplementum* 1979;**626**:34–36.
Helgeland A. Hjermann I. Holme I, Liren P. Serum triglycerides and serum uric acid in untreated and thiazide-

treated patients with mild hypertension. *The American Journal of Medicine* 1978;**64**:34–38.

Helgeland A. Leren P. Foss OP, et al.Serum glucose levels during long-term observation of treated and untreated men with mild hypertension. *The American Journal of Medicine* 1984;**76**:802–805.

Holme I. Coronary risk factors and their possible causal role in the development of coronary heart disease. *Journal Oslo City Hospital* 1982;**32**:79–105.

Holme I. Helgeland A. Hjermann I, et al.Correlates of blood pressure change in middle-aged male mild hypertensives: results from the untreated control group in the Oslo hypertension trial. *American Journal of Epidemiology* 1988; **127**(4):742–52.

Leren P, et al.Oslo hypertension study. *Drugs* 1986;**31** (Suppl 1):41–45.

Leren P, Helgeland A. Coronary heart disease and treatment of hypertension. Some Oslo data. *The American journal of Medicine* 1986;**80**(Suppl 2A):3–6.

Leren P. Eide I. Foss OP, et al.Blood lipids and antihypertensive drugs. *Journal of Pharmacology (Paris)* 1983;**14**(Suppl II):217–20.

Leren P. Hegeland A. Hjermann I, Holme I. The Oslo study: CHD risk factors, socioeconomic influences, and interventions. *American Heart Journal* 1983;**106**: 1200–1206.

USPHSHC ***{published data only}***

Smith WM. Treatment of mild hypertension: results of a ten-year intervention trial. *Circ Res* 1977 May;**40**(5 Suppl 1):I98–105. [PUBMED: 140029]

Additional references

Collins 1990

Collins R, Peto R, Macmahon S, Hebert P, et al.Blood pressure, stroke, and coronary heart disease- Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet* 1990; **335**:827–838.

Gueyffier 1996

Gueyffier F, Froment A, Gouton M. New meta-analysis of treatment trials of hypertension: improving the estimate of therapeutic benefit. *J Human Hyperten* 1996;**10**:1–8.

Mancia 2009

Mancia G, Laurent S, Agabiti-Rosei E, et al.Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *Journal of Hypertension* 2009;**27**:1–38.

Marchant 2011

Marchant I, Nony P, Cucherat M, Boissel J-P, Thomas SR, et al.The Global Risk Approach Should Be Better Applied in French Hypertensive Patients: A Comparison between Simulation and Observation Studies. *PLoS ONE* 2011;**6**(3):e17508. [DOI: e17508. doi:10.1371/ journal.pone.0017508]

Psaty 1997

Psaty BM, Smith NL, Siscovick DS, Koepsell TD, et al.Health outcomes associated with antihypertensive therapies used as first- line agents. A systematic review and meta-analysis. *JAMA* 1997;**277**:739–745.

Psaty 2003

Psaty BM, Lumley T, Furberg CD, Schellenbaum G, Pahor M, Alderman MH, Weiss NS. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. *JAMA* 2003;**289**(19): 2534–2544.

Quan 2000

Quan A, Kerlikowske K, Gueyffier F, Boissel JP, for the INDANA Investigators. Pharmacotherapy for hypertension in women of different races. *Cochrane Database of Systematic Reviews* 2000, Issue 3. [DOI: 10.1002/ 14651858.CD002146]

Therapeutics Initiative 2007

Therapeutics Intitiative. Mild Hypertension- An approach to using evidence in the decision making process. *Therapeutics Letter* Jan–Feb 2007;**62**:1–2.

Wright 1999

Wright JM. Cheng-Han Lee, Chambers KC. Systematic review of antihypertensive therapies: does the evidence assist in choosing a first-line drug?. *CMAJ* 1999;**161**:25–32.

Wright 2009

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

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

ANBP

Methods	Randomised single-blind, comparing treatment with placebo. Trial conducted in Australia
Participants	Ambulatory young patients, with mean age 50 years, range (30-59 years). Australian (White) or European born, the former predominating. Male (63%). Baseline mean SBP/DBP was 157.4/100.4 mmHg. The inclusion criteria was SBP < 200 mmHg and DBP 90-110 mmHg. Patients were followed for 4 years
Interventions	Chlorothiazide 500mg once or twice daily, methyldopa, propranolol, or pindolol added as 2nd-order treatment, and hydralazine or clonidine added as 3rd-order treatment. Control: placebo
Outcomes	Mortality, CHD, stroke, other CV events, systolic BP and diastolic BP
Notes	Attrition bias for ANBPS trial : All components from the composite outcome were terminating events, without complementary mortality survey. All analyses regarding these separated components are subject to a censoring bias

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"patients randomly allocated, with stratification by age and sex" Not enough detail to know how this was done
Allocation concealment (selection bias)	High risk	Inadequate
Blinding (performance bias and detection bias) All outcomes	High risk	Trial was single blind so investigators physicians caring for the patient were not blinded as to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	All components from the composite outcome were terminating events, without complementary mortality survey. All analyses regarding these separated components are subject to a censoring bias
Selective reporting (reporting bias)	Unclear risk	Not specified in report.

MRC

Methods	Randomised single-blind comparing 2 treatments and placebo
Participants	Ambulatory patients, with mean age 52 years, range (35-64 years). Ethnicity not reported. Male (52%). Baseline mean SBP/DBP was 161.4/98.2 mmHg and pulse pressure was 63 mmHg. The inclusion criteria was SBP < 200 mmHg and DBP 90-109 mmHg. Patients were followed for 5 years
Interventions	Bendrofluazide 10 mg daily (71% mono), Propranolol 80-240 mg daily (78% mono), methyldopa added if required. Control: placebo
Outcomes	Mortality, stroke, CHD, systolic BP and diastolic BP
Notes	No CHF data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was in stratified blocks of eight within each sex, 10 year age group, and clinic." Sufficient detail provided to consider low risk
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Trial was single blind. Investigators knew what treatment the patients were receiving
Incomplete outcome data (attrition bias) All outcomes	High risk	Myocardial infarction and stroke were reasons for terminating the study follow-up, except for death flagging. This induces a censoring attrition bias, limited to the occurrence non-fatal events myocardial infarction or stroke. In the original paper : TERMINATION OF PARTICIPATION IN TRIAL Events terminating a patient's participation were: stroke, whether fatal or non-fatal; coronary events, including sudden death thought to be due to a coronary cause, death known to be due to myocardial infarction, and non-fatal myocardial infarction; other cardiovascular events, including deaths due to hypertension (ICD 400-404) and to rupture or dissection of an aortic aneurysm; and death from any other cause. Clinic staff reported these events to the coordinating centre. The records of all patients who suffered non-fatal terminat-

		ing events and of any others who lapsed from the trial, whatever the reason, were "flagged" at the Southport NHS central register to ensure notification of death.)
Selective reporting (reporting bias)	Unclear risk	Not described in report

SHEP

Methods	Randomised, double-blind, placebo controlled. Trial conducted in USA
Participants	Ambulatory patients, with mean age 72 years, range (> 60 years). 13.9% of patients were African-Americans. Male (43%). Baseline mean SBP/DBP was 170/77 mmHg and pulse pressure was 93 mmHg. The inclusion criteria was SBP 160-219 mmHg and DBP <90 mmHg. Patients were followed for 4.5 years
Interventions	Chlorthalidone 12.5-25 mg (69%), Step 2. atenolol 25-50 mg (23%) or reserpine 0.05-0.1 mg. Identical placebo
Outcomes	Mortality, stroke, CHD, CHF, systolic BP and diastolic BP
Notes	Total CVS verified remains same

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Screenees were randomly allocated by the coordinating center to one of two treatment groups. Randomization was stratified by clinical center and by antihypertensive medication status at initial contact."
Allocation concealment (selection bias)	Low risk	Adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of patients and investigators was achieved.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Patients with non-fatal outcomes were not censored.
Selective reporting (reporting bias)	Unclear risk	Not specified in report.

VA-NHLBI

Methods	Randomised, double-blind, placebo controlled. Trial conducted in USA
Participants	Ambulatory patients, with mean age 37.5 years, range (21-50 years). 25% patients were African-Americans. Male (100%). Baseline mean DBP was 93.3 mmHg. The inclusion criteria was DBP 85-105 mmHg. Patients were followed for 2 years. Target < 85 mmHg
Interventions	CHTD 50 mg, 100 mg, (53% CHTD alone). Reserpine 0.25 mg. Control: placebo
Outcomes	Mortality, stroke, CHD, CHF, and diastolic BP
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Use of randomization number and subjects were "randomized in double-blind fashion into active drug therapy and placebo groups"
Allocation concealment (selection bias)	Low risk	Adequate
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding of investigators and patients was achieved.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Selective reporting (reporting bias)	Unclear risk	Not specified

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

Study	Reason for exclusion
COOPE	Only 2 subjects met criteria defined in this review.
FEVER 2005	Not a placebo or no treatment controlled trial.
HDFP	No untreated control group.
MRC2	Only 2 subjects met criteria defined in this review.
MRFIT	No untreated / placebo control group.

(*Continued*)

Oslo	Approximately half of the subjects had moderately elevated BP and data was not available for the subjects with mild elevation of BP separately
USPHSHC	Approximately half of the subjects had moderately elevated BP and data was not available for the subjects with mild elevation of BP separately

DATA AND ANALYSES

Comparison 1. Treatment versus No Treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	4	8912	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.63, 1.15]
2 Stroke	3	7080	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.24, 1.08]
3 Coronary Heart Disease	3	7080	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.80, 1.57]
4 Total CV events	3	7080	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.72, 1.32]
5 Withdrawals due to adverse effects	1	17354	Risk Ratio (M-H, Fixed, 95% CI)	4.80 [4.14, 5.57]

ADDITIONAL TABLES

Table 1. Patient numbers in this review versus total numbers in the trials

Trials	This review		Total	
	Treatment	Placebo	Treatment	Placebo
MRC	3012	3049	8700	8654
ANBP	958	874	1721	1706
SHEP	3	4	2365	2371
VA-NHLBI	508	504	508	504
Total	4481	4431	13294	13235

FEEDBACK

Should mild hypertension be treated? The possible benefits of angiotensin receptor blockers, 12 September 2012

Summary

We read with interest the manuscript of Diao D et al at about the possible benefits of treating mild hypertensive patients in primary prevention. (Diao 2012) In this study, 4 randomized clinical trials, with a total of 8,912 patients, were included for the analysis. After a follow-up of 4-5 years, antihypertensive treatment was not followed with a reduction of total mortality, coronary heart disease, stroke or total cardiovascular events. Even more, antihypertensive treatment was associated with an increased risk of withdrawals due to adverse effects.

Although the implications of this study are of great interest, the fact is it has important limitations that hamper its conclusions to be translated into clinical practice. Firstly, the relative small sample size, with less than 9,000 patients included. Indeed, not many studies have analyzed this population. By contrast, current outstanding clinical trials actually include a greater population to allow attaining clinically relevant conclusions (i.e. in LIFE, 9,193 patients were included (Dahlöf 2002), in ACCOMPLISH, 11,506 patients (Jamerson 2008). This is even more important taking into account that in these studies high risk hypertensive patients were included, with more expected outcomes. As cardiovascular risk lowers, more patients are required to really ascertain whether a treatment is effective or not. Moreover, follow up was limited to 4 to 5 years in the included studies. However, in general, hypertension-related organ damage needs time to establish and more time to develop cardiovascular complications. Moreover, this time is even longer in mild hypertension. Thus, to actually establish the real benefits of antihypertensive therapy in this population, longer follow-up is warranted or at least, intermediate endpoints, such as left ventricular hypertrophy or microalbuminuria, should be analyzed (Mancia 2009).

Finally, it is also important to analyze the antihypertensive therapy used in the studies included in this meta-analysis (ANBP: chlorothiazide, methyldopa, propranolol, or pindolol added as 2nd-order treatment, and hydralazine or clonidine added as 3rd-order treatment; control placebo; MRC: bendrofluazide, propranolol, methyldopa added if required; control placebo; SHEP: chlorthalidone, step 2 atenolol or reserpine; identical placebo; VA-NHLBI: chlortalidone, reserpine; control placebo) (Diao D 2012). Many of these drugs are not currently being used. In fact, modern antihypertensive agents are more effective or better tolerated than those used in most of these studies.

On the other hand, beta blockers (present in all the analyzed studies) are commonly withdrawn due to side effects in a significant proportion of patients. This fact occurs even in secondary prevention (Gislason 2006). Medication adherence is important to assure the benefits of therapy during follow-up. In fact, when the efficacy of 2 drugs is similar, the agent with lesser rates of side effects should be chosen. For example, in the ONTARGET trial, although telmisartan and ramipril similarly reduced cardiovascular outcomes, when discontinuation of study medication was included in the analysis, a trend to lesser outcomes was observed with telmisartan (Barrios 2008). If using drugs with lower side effects is important in secondary prevention, this is even more relevant in primary prevention where patients do not have symptoms. With regard to first-line current antihypertensive drugs (diuretics, beta blockers, calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers), it seems that angiotensin receptor blockers could be the better tolerated agents.

Although specific and appropriate clinical trials are needed to ascertain the benefits of antihypertensive therapy in patients with mild hypertension, it should be currently recommended to reduce blood pressure values to established targets in patients with mild hypertension, but with those drugs better tolerated.

References

1. Barrios V, Escobar C, Prieto L, Herranz I. Adverse events in clinical trials: is a new approach needed? Lancet. 2008;372(9638): 535-6.

2. Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359(9311):995-1003.

3. Diao D, Wright JM, Cundiff DK, Gueyffier F. Pharmacotherapy for mild hypertension. Cochrane Database Syst Rev. 2012;8: CD006742.

4. Gislason GH, Rasmussen JN, Abildstrøm SZ, Gadsbøll N, Buch P, Friberg J, Rasmussen S, Køber L, Stender S, Madsen M, Torp-Pedersen C. Long-term compliance with beta-blockers, angiotensin-converting enzyme inhibitors, and statins after acute myocardial infarction. Eur Heart J. 2006;27(10):1153-8.

5. Jamerson K, Weber MA, Bakris GL, Dahlöf B, Pitt B, Shi V, Hester A, Gupte J, Gatlin M, Velazquez EJ; ACCOMPLISH Trial Investigators. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med. 2008;359(23):2417-28.

6. Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, Cifkova R, Clément D, Coca A, Dominiczak A, Erdine S, Fagard R, Farsang C, Grassi G, Haller H, Heagerty A, Kjeldsen SE, Kiowski W, Mallion JM, Manolis A, Narkiewicz K, Nilsson P, Olsen MH, Rahn KH, Redon J, Rodicio J, Ruilope L, Schmieder RE, Struijker-Boudier HA, van Zwieten PA, Viigimaa M, Zanchetti A; European Society of Hypertension. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. J Hypertens. 2009;27(11):2121-58.
We agree with the conflict of interest statement below:

We certify that we have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of our feedback.

Reply

We thank Drs. Barrios and Escobar for their comments.
Regarding the number of RCT participants included in this systematic review (n=8,912), we agree that it would be good if there were more data, however, this review does represent all the participants and data that are available at this time. Thus at the present time we do not have proof that the benefits of drug treatment outweigh the harms for primary prevention patients with mild elevations in blood pressure, a group that represents half of the hypertensive population.
We agree with Barrios and Escobar's conclusions that "specific and appropriate clinical trials are needed to ascertain the benefits of antihypertensive therapy in patients with mild hypertension". However, we disagree with their conclusions that "it should be currently recommended to reduce blood pressure values to established targets in patients with mild hypertension, but with those drugs better tolerated". Widespread treatment in the absence of evidence is never a good approach. Patients who are offered drug treatment need to be told that drug treatment has not been proven to be beneficial.

Contributors

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WHAT'S NEW

Last assessed as up-to-date: 1 October 2011.

Date	Event	Description
12 September 2012	Feedback has been incorporated	Comment: Should mild hypertension be treated?

HISTORY

Protocol first published: Issue 3, 2007

Review first published: Issue 8, 2012

CONTRIBUTIONS OF AUTHORS

FG provided the data from the INDANA database for the specific population of interest. JMW, DD, FG were responsible for deciding trials to be included. DD and JMW were responsible for data entry and DD wrote the initial draft. DKC suggested the topic for the review and edited the manuscript. All authors were responsible for interpreting the data and reviewing the final draft.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Department of Anesthesiology, Pharmacology & Therapeutics, University of British Columbia, Canada.
- Clinical Pharmacology Department, Hospices Civils de Lyon, France.
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- Claude Bernard University Lyon I, France.
- BIMBO project, SYSCOMM 2008 Nr 002, ANR- www.agence-nationale-recherche.fr, France.

External sources

- CIHR Grant to the Hypertension Review Group, Canada.
- British Columbia Ministry of Health Grant to the Therapeutics Initiative, Canada.

INDEX TERMS

Medical Subject Headings (MeSH)

Antihypertensive Agents [adverse effects; *therapeutic use]; Blood Pressure [drug effects]; Coronary Disease [prevention & control]; Hypertension [*drug therapy; mortality]; Medication Adherence [statistics & numerical data]; Randomized Controlled Trials as Topic; Stroke [prevention & control]

MeSH check words

Adult; Humans