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PHARMACOTHERAPY FOR HYPERTENSION IN THE ELDERLY

Musini Vijaya M, Tejani Aaron M, Bassett Ken, Wright James M

Musini Vijaya M, Tejani Aaron M, Bassett Ken, Wright James M

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ABSTRACT

Background

Elevated blood pressure (known as hypertension) increases with age, and most rapidly over age 60. Systolic hypertension is more strongly associated with cardiovascular disease than diastolic hypertension, and occurs more commonly in older people. It is important to know the benefits and harms of antihypertensive treatment of hypertension in this age group.

Objective

To quantify antihypertensive drug effect on overall mortality, cardiovascular mortality and morbidity and withdrawal due to adverse effects in people 60 years and older with mild to moderate systolic or diastolic hypertension.

Criteria for considering studies for this review

Updated search of electronic database of EMBASE, CENTRAL, MEDLINE until Dec 2008; previous search of two Japanese databases (1973-1995) and WHO-ISH Collaboration register (August 1997); references from reviews, trials and previously published meta-analyses; and experts.

Selection criteria

Randomized controlled trials of at least one year duration in hypertensive elders (at least 60 years old) comparing antihypertensive drug therapy with placebo or no treatment and providing morbidity and mortality data.

Data collection and analysis

Outcomes assessed were total mortality (including cardiovascular, coronary heart disease and cerebrovascular mortality); total cardiovascular morbidity and mortality (representing combined coronary heart disease and cerebrovascular morbidity and mortality); and withdrawal due to adverse events.

Main results

Fifteen trials (24,055 subjects ≥ 60 years) with moderate to severe hypertension were identified. These trials mostly evaluated first-line thiazide diuretic therapy for a mean duration of treatment of 4.5 years. Treatment reduced total mortality, RR 0.90 (0.84, 0.97); event rates per 1000 participants reduced from 116 to 104. Treatment also reduced total cardiovascular morbidity and mortality, RR 0.72 (0.68, 0.77); event rates per 1000 participants reduced from 149 to 106. In the three trials restricted to persons with isolated systolic hypertension the benefit was similar. In very elderly patients ≥ 80 years the reduction in total cardiovascular mortality and morbidity was

similar RR 0.75 [0.65, 0.87] however, there was no reduction in total mortality, RR 1.01 [0.90, 1.13]. Withdrawals due to adverse effects were increased with treatment, RR 1.71 [1.45, 2.00].

Authors' conclusions

Treating healthy persons (60 years or older) with moderate to severe systolic and/or diastolic hypertension reduces all cause mortality and cardiovascular morbidity and mortality. The decrease in all cause mortality was limited to persons 60 to 80 years of age.

PLAIN LANGUAGE SUMMARY

Hypertension (high blood pressure) is common among elderly people and increases the risk of heart attack and stroke. An assessment of all the trials of blood pressure lowering therapy in people with hypertension 60 years and over showed that treatment reduced death, strokes and heart attacks. The benefit was similar if both the upper and lower number was elevated or only the upper number. In people 80 and over treatment did not reduce death but did reduce stroke.

WHAT'S NEW

What's new
Last assessed as up-to-date: 31 May 2009.

Date	Event	Description
1 November 2010	Amended	Added links to Figures in the result section (to the Forest plots of the primary and secondary outcome measures) which were initially refered to as links in the Data and Analysis section.
27 October 2009	Amended	Corrected denominator of the STOP trial for total mortality from 22 to 122 in the hypertension in very elderly subgroup

BACKGROUND

Blood pressure increases with age, and the rate of rise is greater over age 60. As a result the number of people with elevated blood pressure (known as hypertension) increases with age. Systolic blood pressure is more strongly associated with cardiovascular disease than diastolic blood pressure particularly in older people. Isolated systolic hypertension occurs more commonly in older people. Older people also accumulate higher rates of other risk factors for cardiovascular disease including obesity, left ventricular hypertrophy, sedentary life style, hyperlipidemia, and diabetes.

Most of the early trials evaluating antihypertensive drug therapy were conducted in lower risk people under age 60. The first definitive clinical trial evidence supporting blood pressure lowering treatment was produced in the mid-1980s. Before that time, policymakers and clinicians were reluctant to recommend treatment particularly in the elderly; some regarded systolic hypertension as a natural feature of aging, while others feared excessive harm from blood pressure lowering in this age group.

Since 1985, several large trials have been conducted, and several meta-analyses have summarized their results (Davidson 1987 , Staessen 1988 , Staessen 1990a , Staessen 1990b , Leonetti 1992 , Thijs 1992 , Celis 1993 , MacMahon 1993 , Thijs 1994 , Insua 1994 , Pearce 1995 , Wright JM 1999 , Gueyffier F 1999 , HYVET P 2003 , HYVET 2008 , Musini VM 2008). The purpose of this systematic review is to summarize all the available evidence for the benefits and harms of antihypertensive treatment for people aged 60 and above.

OBJECTIVES

Primary:

1. To quantify antihypertensive drug effect on overall mortality in people 60 years and older with mild to moderate systolic or diastolic hypertension.

Secondary:

2. To quantify antihypertensive drug effect on cardiovascular specific morbidity and mortality in people 60 years and older with mild to moderate systolic or diastolic hypertension.

3. To quantify withdrawal due adverse events.

Planned subgroup analyses included patients with isolated systolic hypertension and the very elderly people 80 years or older.

METHODS OF THE REVIEW

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Only randomized controlled trials of at least one year duration were included. Trials must have included a control group that either received a placebo or received no anti-hypertensive therapy. Trials that compared two specific antihypertensive therapies were excluded.

Types of participants

Trials must include only people 60 or older or separately report outcomes for people 60 or older. Participants must have a systolic blood pressure of at least 140 mmHg and/or a diastolic blood pressure of at least 90 mmHg at baseline.

Types of intervention

Acceptable anti-hypertensive drug therapies include: angiotensin converting enzyme inhibitors, angiotensin receptor antagonists, beta adrenergic blockers, combined alpha and beta blockers, calcium-channel blockers, diuretics, alpha adrenergic blockers, central sympatholytics, direct vasodilators or peripheral adrenergic antagonists. Drugs could have been administered alone or in combination or in fixed or stepped up regimens.

Types of outcome measures

Morbidity and mortality were defined as follows:

Total mortality means deaths from all causes.

Coronary heart disease (CHD) mortality includes fatal myocardial infarctions and sudden or rapid cardiac death.

Cerebrovascular mortality includes fatal strokes.

Cardiovascular mortality sums coronary heart disease mortality and cerebrovascular mortality.

CHD morbidity and mortality includes fatal and non fatal myocardial infarctions and sudden or rapid cardiac death.

Cerebrovascular morbidity and mortality includes fatal and nonfatal strokes.

Cardiovascular morbidity and mortality includes CHD plus cerebrovascular morbidity and mortality plus aneurysms, congestive heart failure and transient ischemic attacks.

Withdrawal due to adverse effects

When the primary trials did not report outcomes with exact definitions as listed above, the review authors categorized data to minimize missing data while maintaining the intended study measures. For example, the Medical Research Council Trial of Treatment of Hypertension in Older Adults (MRCOA) includes "deaths due to hypertension" in its definition of "cardiovascular events". The broad label "deaths due to hypertension" is not included in the standard definition for "cardiovascular morbidity and mortality" listed above. We include MRCOA's results in the cardiovascular morbidity and mortality outcome measure because "deaths due to hypertension" was congruous with the concept of cardiovascular morbidity and mortality. The alternative, omitting MRCOA's data, would result in a more reliable measure but at the expense of accuracy of the effect estimate. The number of differences in definitions was small and is unlikely to affect results. Supporting this assumption, previous meta-analyses found homogeneity of risk reduction among outcome measures suggesting differences in outcome definition were unlikely causes of bias.

One of the new trials included in the update (HYVET P 2003) was not conducted according to the standards of Good Clinical Practice Guidelines and did not collect data on serious adverse events, non-fatal MI or heart failure (personal communication with the author). However, data on cardiovascular mortality and morbidity was reported in the trial and is included in the meta-analysis.

The actual endpoints represented by each outcome measure for each study are listed under the "Outcomes" heading of the Characteristics of included studies table. Within each study the definition of endpoints for each outcome measure are identical between the treatment and control groups. The individual non-fatal outcomes included in the composite endpoint were included as counted by the trialist of each study. Many trials did not report on how events were counted after patients were

censored. Refer to personal communication with author of HYVET 2008 trial in the risk of bias table to find out how events were counted in that trial.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

Search methods for identification of studies

The following sources were searched:

Updated search of MEDLINE up to Dec. 2008, EMBASE (up to Dec. 2008), CENTRAL (up to Dec. 2008, issue 4). The previous version of this review included search of two Japanese databases: JMEDICINE was searched in the previous review from 1981-1995 and JAPIC-DOC from 1973-1995 with the keywords Hikaku-Shiken (comparative studies), Nijuu-Mouken-Ho (double-blind method) and Hontaisei-Koketsuatsu (hypertension). This search produced 46 articles of which 34 were reports of randomized controlled trials. Titles of the 34 RCTs were translated into English by S Lee-Borges. The abstracts of three possibly relevant trials were translated into English. None met the inclusion criteria of this review.

Thirteen other meta-analyses on antihypertensive drug therapy in the elderly have also been published (Davidson 1987 , Staessen 1988 , Staessen 1990a , Staessen 1990b , Leonetti 1992 , Thijs 1992 , Celis 1993 , MacMahon 1993 , Thijs 1994 , Pearce 1995 , Wright JM 1999 , Gueyffier F 1999 , Musini VM 2008). A review of the reference lists in these review did not identify any additional studies which met the inclusion criteria for this review.

The MEDLINE search has been updated by searching from 1994 through December 2008. The search strategy (Appendix 1) is designed to identify pharmacological treatment of hypertension. (A "/" at the end of a term indicates that it is a Medical Subject Heading (MeSH) term; "exp" indicates that the term is exploded meaning that all MeSH terms nested under the exploded MeSH term are included in the search; "tw" indicates that the term is a text word meaning the title, abstract and MeSH terms are searched for the term; hypertension/dt returns references coded as Drug Treatment for hypertension; "pt" indicates a publication type; "ti.ab" indicates a search for the text word in the title and abstract but not the MeSH terms; the symbols "$" and "?" are wildcard characters used to search for multiple forms of a word; the search modifier "adj" plus a number between any two terms returns records which contain the two terms within the specified number of words of each other.)

The updated search of Medline up to December 2008 identified 162 citations. The titles and abstracts of this list were screened independently by two reviewers (VM and AT) for inclusion which resulted in the retreival of 31 full papers. One reviewer then screened the 31 full papers and a further 3 RCTS were considered for potential inclusion into the review (Jikei 2007 , ADVANCE 2007 , SCOPE 2003). Three reviewers discussed and reached consensus that the 3 RCTS did not meet the inclusion criteria and were excluded. A search of CENTRAL up to June 2009 identified only 1 additional citation (HYVET-Cog 2008) that was not identified in the Medline search. The HYVET-Cog 2008 was retrieved however it was concluded that this substudy of the HYVET 2008 trial did not provide any additional data for analysis. A search of EMBASE was conducted up to December 2008 which identified 6 new citations however none of these met inclusion criteria based on a review of titles and abstracts.

Bibliographies of newly identified meta-analyses, reviews and trials were examined for references to other trials.

DATA COLLECTION AND ANALYSIS

Data collection and analysis

Data abstraction

This review is based on five previously published meta-analyses on the same topic (Mulrow 1994 , Mulrow 1998 , Wright JM 1999 , Gueyffier F 1999 , Musini VM 2008). Data was abstracted using a standard data abstraction form; dual abstraction of data from the original reports of trial results by two independent reviewers; and disagreements were resolved by discussion. The published results of these meta-analyses as well as data from additional trials included in the updated review were compared by two reviewers (VM and AT). Any disagreements were resolved by consensus (JMW and KB) .

Risk of Bias table

A quality scoring scheme was not used, but instead key trial characteristics are detailed in the table Characteristics of included studies . Potential parameters of methodological quality listed in the table include: whether randomization was completed in an appropriate and blinded manner; whether patients, providers and/or outcome assessors were blinded to assigned therapy; whether the control group received a placebo; percent of participants who did not complete follow-up (dropouts); and the percent of participants not on assigned active or placebo therapy at study completion (cross-over).

The updated review uses the Risk of Bias tool to assess each trial according to the Cochrane Handbook guidelines.

Analyses

Quantitative analyses of outcomes are based on intention-to-treat results. Our measure of effect for each study was the Relative-Risk (RR) with 95% CI. Chi-square tests for heterogeneity were used to assess outcome data for compatibility with the assumption of a uniform relative risk (P>0.10). Pooled risk differences are converted to numbers needed to treat (NNTs) with the formula NNT = 1/risk difference. NNTs are the number of patients who must be treated to prevent one adverse outcome.

To test for robustness of results, several sensitivity analyses were performed. Data were analysed using both fixed effect and random effects models. As further tests of sensitivity, trials that were not blinded and placebo controlled were analysed separately from blinded (subject and/or provider), placebo controlled trials. Results were also analysed with and without those trials restricted to persons who had previously suffered a stroke. Results of trials restricted to persons with isolated systolic hypertension were analysed both as a separate group and combined with trials also assessing persons with both systolic and diastolic hypertension. Analyses in the very elderly (80 year or older) were planned because a subgroup meta-analysis from earlier trials by Gueyffier F 1999 showed a trend towards increased mortality. Furthermore, two recent randomised trials HYVET P 2003 and HYVET 2008 were specifically done in the very elderly group of patients.

Individual differences in patient characteristics or disease severity are associated with different levels of risk to experience an adverse event. In the aggregate, these individual differences contribute to the proportion of patients we expect to experience an event within a population. Variation in level of risk in different patient populations, both within and between clinical trials, is often associated with variability in treatment outcomes (Ioannidis 1997 , Schmid 1998). This average population risk is unknown, but contributes to the proportion of events experienced by a placebo control group in a randomised trial. We use the term control rate to describe the probability that a member within the control group experiences the adverse event, and we use this sample value to estimate the aggregate population risk for patients enrolled in a clinical trial.

METHODOLOGICAL QUALITY

RESULTS

Results

Description of studies

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

Two new randomised controlled trials met the inclusion criteria (HYVET 2008 and HYVET P 2003). Two RCTs included in the previous version were excluded in the update since the control group was not an untreated or placebo control group. The HDFP 1982 study was excluded since it is a multifactorial intervention (Ebrahim 2006). CASTEL 1994 was excluded since the control group was receiving non-specific anti-hypertensive therapy from their personal physician.

Fifteen trials including 24,005 people age 60 or over were identified. For most subjects included in this review the mean age ranged from 63 to 84 years. Three trials (Carter 1970 , HTN Coop 1974 , VA Coop 1970) did not report mean age. Most trials were conducted in Western, industrialized countries and evaluated first-line diuretics (ANBP 1981 , Carter 1970 , EWPHE 1989 , HYVET 2008 , HYVET P 2003 , Kuramoto 1981 , MRCOA 1992 , SHEP 1991 , SHEP-PS 1986 , VA Coop 1970). Two trials evaluated beta-blocker therapies (HEP 1986 , STOP 1991). Four of these trials (Carter 1970 , VA Coop 1970 , HTN Coop 1974 , ANBP 1981) originally included both younger and older persons. Only data on those older than 60 is reported. The average age across trials was 73.8 years. The Swedish Trial in Old Patients with Hypertension (STOP 1991) specifically evaluated people over age 70. The HYVET P 2003 and HYVET 2008 trials included patients 80 years or older.

Participants were recruited from industrialized countries: USA (36%), UK (25%), European multi-site trials (25%), Sweden (7%), Italy (3%), Australia (3%) and Japan (<1%). HYVET P 2003 trial recruited patients from Bulgaria (88%), Spain (3%), Romania (3%), UK (2.5%) and Poland (1.5%) and from other countries in smaller numbers (Finland, Lithuania, Ireland, Greece and Serbia). HYVET 2008 trial recruited patients from Western Europe (2.2%), Eastern Europe (55.8%), China (39.6%), Australasia (0.5%) and Tunisia (1.9%).

14,663 (59.5%) percent of the subjects were female. The four trials based in the USA reported ethnicity African-American: SHEP 1991 (14%), SHEP-PS 1986 (18% non-white), VA Coop 1970 (41%), HTN Coop 1974 (78%). The ethnicity data from VA Coop 1970 and HTN Coop 1974 refer to the entire study population, not the >60 year old sub-group. All subjects in ANBP 1981 and STOP 1991 were white. Nine trials including HYVET P 2003 and HYVET 2008 did not report ethnicity.

Study populations predominantly consisted of ambulatory patients recruited from the community or primary care facilities. A small proportion (6%) were recruited from hospitals or homes for the aged. Studies did not consistently report data on pre-existing conditions for subjects; available data follows. Two small studies were limited to stroke survivors (Carter 1970 , HTN Coop 1974). Six other trials reported the baseline prevalence of stroke. The sample-size-based weighted average prevalence across those six trials was 3.6%: SHEP-PS 1986 (1%), SHEP 1991 (1.4%), Syst-Eur 1991 (3.5%), Sprackling 1981 (11.3%), HYVET P 2003 (4.5%) and HYVET 2008 (6.8%). Six trials reported the baseline prevalence of myocardial infarctions. The average prevalence across trials was 2.3%: ANBP 1981 (0.5%), Syst-Eur 1991 (1.2%), SHEP-PS 1986 (4%), SHEP 1991 (4.9%), HYVET P 2003 (3.0%), and HYVET 2008 (3.1%). Two studies excluded patients with diabetes (ANBP 1981 , MRCOA 1992), while three other trials reported the baseline prevalence. The average prevalence across trials was 9.2%: HYVET 2008 (6.8%), SHEP 1991 (10.1%), HTN Coop 1974 (36%). Two trials reported the baseline prevalence of hyperlipidemia: HTN Coop 1974 (22%) and ANBP 1981 (62.2%). Ten trials reported the baseline prevalence of smoking. The average prevalence across trials was 12.1%: HYVET P 2003 (4.2%), HYVET 2008 (6.6%), Syst-Eur 1991 (7.3%), SHEP-PS 1986 (11%), SHEP 1991 (12.7%), EWPHE 1989 (16.4%), ANBP 1981 (17.5%), MRCOA 1992 (17.5%), HEP 1986 (24%), and HTN Coop 1974 (60%). Only HTN Coop 1974 reported data on prevalence of obesity (29%).

Entry diastolic blood pressure criteria also have varied somewhat from trial to trial. However, trials in older persons have not routinely included patients with higher diastolic blood pressures than trials in younger persons.

All trials except Carter 1970 reported the mean SBP and DBP at baseline. SHEP-PS 1986 , SHEP 1991 and Syst-Eur 1991 restricted recruitment to persons with isolated systolic hypertension; defined as SBP 160-219 mm Hg and DBP <90 mm Hg (SHEP 1991 , SHEP-PS 1986) or DBP < 95 mm Hg (Syst-Eur 1991). Mean blood pressure at entry in the 3 isolated systolic hypertension trials was 172/81 mmHg. Two studies (Carter 1970 , HEP 1986) recruited persons with isolated systolic hypertension, diastolic hypertension or systo-diastolic hypertension. Kuramoto 1981 and MRCOA 1992 recruited patients with either isolated systolic hypertension or systo-diastolic hypertension. HYVET P 2003 recruited patients with systolic and/or diastolic hypertension (SBP > 140 mmHg and DBP 90-109 mmHg). HYVET 2008 recruited patients with persistent hypertension defined as SBP of 160-199 mmHg and a DBP < 110mmHg. 32.5% of patients in HYVET 2008 had isolated systolic hypertension. The remainder of the studies required that subjects' DBP be at least 90 mm Hg. Mean BP at entry in these 11 other trials was 182/95 mmHg.

See the "Participants" heading in the Characteristics of included studies table for a complete description of each study's blood pressure inclusion criteria. The mean sitting SBP/DBP in HYVET P 2003 was 182/99.6 mmHg and in HYVET 2008 was 173/90.8 mmHg.

Twelve of the 15 trials instituted a stepped care approach to hypertension treatment. In over 70% of trials a thiazide diuretic was the first line drug in the treatment group. Seven trials (Carter 1970 , ANBP 1981 , Kuramoto 1981 , SHEP-PS 1986 , EWPHE 1989 , SHEP 1991 , HYVET 2008) started the treatment group exclusively on a thiazide diuretic. HEP 1986 and STOP 1991 started the treatment group on either a diuretic or beta-blocker. MRCOA 1992 randomized the treatment group to two arms, one initially receiving diuretics and the other initially receiving a beta-blocker. Syst-Eur 1991 started the treatment group on a calcium channel blocker. HYVET P 2003 started one treatment arm on a diuretic and other treatment arm with an ACE inhibitor. Second and third line drugs included diuretics, beta-blockers, central acting anti adrenergic agents, peripheral acting anti adrenergic agents, vasodilators, converting-enzyme inhibitors and calcium channel blockers. See the "Interventions" heading in the Characteristics of included studies table for a complete description of each study's drug treatment protocol.

Three trials maintained subjects on a particular therapeutic regimen (i.e. not stepped care) throughout the study. VA Coop 1970 treated subjects with a combination diuretic - central acting anti adrenergic agent (hydrochlorothiazide/reserpine) plus a vasodilator (hydralazine). HTN Coop 1974 treated subjects with a diuretic (methyclothiazide) and peripheral acting anti adrenergic agent (deserpidine). Sprackling 1981 treated subjects with a central acting anti adrenergic agent (methyldopa).

HYVET P 2003 trial randomized patients to three groups: no treatment, diuretic based treatment (usually bendrofluazide 2.5mg) and an ACE-inhibitor based regimen (usually lisinopril 2.5mg). To attain target blood pressure (sitting SBP < 150 mmHg and sitting DBP < 80 mmHg) in the actively treated groups, the dose of diuretic or ACEI could be doubled (step 2), diltiazem slow release 120 mg could be added (step 3) and diltiazem slow release 240mg could be added as (Step 4).

HYVET 2008 trial randomized patients to either indapamide sustained release 1.5 mg or matching placebo. In order to reach target blood pressure (SBP < 150 mmHg and DBP < 80 mmHg) perindropil 2 mg or 4 mg or matching placebo could be added.

Length of study follow up ranged from relatively short: 1 year (HYVET P 2003) or 2 years (STOP 1991 , Syst-Eur 1991 , HYVET 2008), to relatively long: the rest of the trials lasting 3 to 6 years. All of the trials were multi site studies except for Carter 1970 and Kuramoto 1981 . The mean duration of treatment was 4.5 years in elderly (60 years or older) and 2.2 years in very elderly patients (80 years or older) and 3.2 years in trials with isolated systolic hypertension in the elderly.

Risk of bias in included studies

Twelve of the 15 trials employed some method of blinding. Twelve blinded subjects to therapy (VA Coop 1970 , HTN Coop 1974 , ANBP 1981 , Kuramoto 1981 , HEP 1986 , SHEP-PS 1986 , EWPHE 1989 , SHEP 1991 , STOP 1991 , MRCOA 1992 , Syst-Eur 1991 , HYVET 2008). Of these, eleven (all but MRCOA 1992) also blinded providers to therapy. Eight trials specifically reported blinding outcome assessors (HEP 1986 , SHEP-PS 1986 , EWPHE 1989 , SHEP 1991 , STOP 1991 , MRCOA 1992 , Syst-Eur 1991 , HYVET 2008).

Eleven trials were placebo controlled (VA Coop 1970 , HTN Coop 1974 , ANBP 1981 , Kuramoto 1981 , SHEP-PS 1986 , EWPHE 1989 , SHEP 1991 , STOP 1991 , MRCOA 1992 , Syst-Eur 1991 , HYVET 2008) . Four trials were no treatment controlled without placebo (Carter 1970 , Sprackling 1981 , HEP 1986 , HYVET P 2003).

In nine of the trials the method of randomization is described while in the remaining six trials randomization is mentioned, but not described. See the "Method" heading in the Characteristics of included studies table for a description of each study's method of randomization and stratification, if any.

Nine studies reported loss to follow-up figures of less than 5% (Carter 1970 , ANBP 1981 , Sprackling 1981 , SHEP-PS 1986 , SHEP 1991 , STOP 1991 , Syst-Eur 1991 , HYVET P 2003 , HYVET 2008). Three studies reported loss to follow-up figures of 13-15% (VA Coop 1970 , Kuramoto 1981 , EWPHE 1989). MRCOA 1992 experienced a loss to follow-up of 25%. The remainder (HTN Coop 1974 , HEP 1986) did not report data on numbers lost to follow-up.

Studies included in this review allowed subjects in the control group to receive antihypertensive therapy because their blood pressure exceeded pre-set "escape" criteria. Also, a portion of the subjects assigned to the treatment group stopped taking their assigned medication because of adverse drug effects or because they achieved normal blood pressures. The degree to which subjects cross over from one group to the other dilutes the results of the study. The percent of patients assigned to the control group which were receiving antihypertensive medication by the end of the trial were as follows: HEP 1986 (9%), Kuramoto 1981 (17%), STOP 1991 (23%), Syst-Eur 1991 (27%), ANBP 1981 (35%), SHEP-PS 1986 (40%), SHEP 1991 (44%), MRCOA 1992 (53%), and EWPHE 1989 (>35%), HYVET P 2003 (0.8%) and HYVET 2008 (0.6%). The remaining four trials did not report such data. The percent of patients assigned to the treatment group which had ceased taking antihypertensive medication by the end of the trial were: HYVET P 2003 (4%), HYVET 2008 (0.5%), HEP 1986 (5%), SHEP 1991 (10%), STOP 1991 (16%), Syst-Eur 1991 (18%), SHEP-PS 1986 (30%), ANBP 1981 (33%), MRCOA 1992 - diuretic arm (48%), MRCOA 1992 - beta-blocker arm (63%), and EWPHE 1989 (>35%). The remaining five trials did not report such data.

and show a summary of the Risk of Bias assessment.

Effects of interventions

See: Summary of findings for the main comparison Antihypertensive drug therapy compared to control in elderly (60 years or older) for hypertension in the elderly ; Summary of findings 2 Antihypertensive drug therapy compared to control in very elderly 80 years or older for hypertension

Analyses were performed on the combined results of all 15 studies. The three trials that included only people with isolated systolic hypertension (SHEP-PS 1986 , SHEP 1991 , Syst-Eur 1991) were included in the overall analyses and were also analysed separately. EWPHE 1989 reported intention-to-treat data for mortality only; the morbidity data reported from EWPHE 1989 is not intention-to-treat and is not included in the analysis. The occurrence of any trial endpoint in ANBP 1981 participants terminated their participation in the study. Thus, true intention-to-treat data for ANBP 1981 is only available for combined cardiovascular morbidity and mortality.

Results were analysed with and without the two small trials that were restricted to stroke survivors (Carter 1970 , HTN Coop 1974). Removing these two trials from the analysis did not appreciably affect the results. The relative risk point estimates and confidence intervals did not shift by more than 0.01. Thus, all results reported below include these two trials.

There was homogeneity across studies with respect to all outcomes except cardiovascular morbidity and mortality. Point estimates for the pooled log relative risk ratios were nearly identical between the random and fixed effect analyses. Thus, all results are reported using the fixed effects model. In the very elderly patients there was homogeneity across studies for all outcomes except total mortality.

Total mortality: The combined results of the 12 trials reporting total mortality data in people 60 years or older show a significant benefit (RR=0.90, 95% CI 0.84 to 0.97; NNT=84) with event rates per 1000 participants reduced from 116 to 104 events with 95% CI of the difference (3 to 19) for a mean duration of treatment of 4.5 years, see . STOP 1991 and HYVET 2008 independently reached a statistically significant mortality benefit.

Analysis of trials in very elderly (80 years or older) showed no reduction in total mortality for a mean duration of treatment of 2.2 years (RR = 0.98 95% CI 0.87 to 1.10; p = 0.72), see . There was significant heterogeneity between trials (RR = 1.06 95% CI 0.88 to 1.28 using random effects model).

The three trials with isolated systolic hypertension did not achieve a statistically significant reduction in mortality for a mean duration of treatment of 3.2 years (RR=0.88, 95% CI 0.77 to 1.01; p =0.07), see .

Cardiovascular mortality: The combined results of the 10 trials reporting cardiovascular mortality data in people 60 years or older indicated a significant reduction (RR=0.77, 95% CI 0.68 to 0.86; ARR= 1.5%, NNT = 67), see . EWPHE 1989 and STOP 1991 independently reached statistical significance. Non-cardiovascular mortality was not affected, RR with 95% CI 1.02(0.92, 1.14 p = 0.65), see .

Combined results of the three trials with isolated systolic hypertension showed a significant reduction in cardiovascular mortality (RR=0.77, 95% CI 0.63 to 0.95), see . Analysis of trials in very elderly (80 years or older) showed no significant difference (RR = 0.98 95% CI 0.81 to 1.19; p = 0.86), see .

Cerebrovascular mortality: In people 60 years or older there was a significant reduction (RR=0.66, 95% CI 0.53 to 0.82), see . STOP 1991 and HEP 1986 independently reached statistical significance.

In the three trials with isolated systolic hypertension the reduction was not statistically significant (RR=0.68 95% CI 0.42 to 1.11; p = 0.13), see .

In the very elderly (80 years or older) there was also no significant difference (RR = 0.80 95% CI 0.58 to 1.11; p = 0.18), see .

Coronary heart disease (CHD) mortality: In the 9 trials reporting CHD mortality in people 60 years or older treatment reduced CHD mortality (RR=0.77, 95% CI 0.65 to 0.90), see . EWPHE 1989 independently reached statistical significance.

In the very elderly (80 years or older) there was no reduction (RR = 0.98 95% CI 0.69 to 1.40; p = 0.93), see .

In the three trials with isolated systolic hypertension the reduction was not statistically significant (RR=0.78, 95% CI 0.60 to 1.02; p = 0.06), see .

Cardiovascular mortality and morbidity (M&M): In the 13 trials reporting cardiovascular mortality and morbidity data in people 60 years or older, treatment caused a significant reduction (RR=0.72, 95% CI 0.68 to 0.77), see . HEP 1986 , HYVET 2008 , MRCOA 1992 , SHEP 1991 , STOP 1991 , Syst-Eur 1991 and VA Coop 1962 independently reached statistical significance. The significant heterogeneity between trials was no longer evident when the unblinded HEP 1986 and Sprackling 1981 trials were excluded from the analysis (RR = 0.71 95% CI 0.66 to 0.78 with I2 reduced from 70% with p < 0.0001 to I2 = 32% with p = 0.14).

Excluding MRCOA 1992 because it used a different definition for the cardiovascular morbidity and mortality outcome did not affect the estimate (RR=0.69, 95% CI 0.65 to 0.75).

Cardiovascular mortality and morbidity was significantly reduced in elderly patients due to reduction in both cerebrovascular as well as CHD mortality and morbidity, see and respectively.

In the very elderly patients (80 years or older) and in elderly patients with isolated systolic hypertension, treatment caused a significant reduction in cardiovascular mortality and morbidity (RR = 0.75 95% CI 0.65 to 0.87 p = 0.0001), see , and (RR=0.68, 95% CI 0.61 to 0.75) see respectively.

Cerebrovascular mortality and morbidity was significantly reduced in the very elderly but there was no significant difference observed in coronary heart disease mortality and morbidity ( ).

Cerebrovascular mortality and morbidity (_) as well as coronary heart disease mortality and morbidity (_) were significantly reduced in the elderly patients with isolated systolic hypertension.

Withdrawals due to adverse effects: Numbers of participants who dropped out of trials due to adverse drug effects were often not reported. The three trials that did report this data showed a significant increase in withdrawals due to adverse effects, RR=1.71, 95% CI 1.45 to 2.00, see , with event rates per 1000 participants increased from 65 to 111 events, absolute risk increase of 46 (95% CI 29 to 65).

The number of people withdrawing from therapy due to adverse effects varied significantly from study to study. On average, treating 17 subjects in SHEP 1991 resulted in one withdrawal, whereas in MRCOA 1992 treating 9 subjects with a diuretic and 4 subjects with a beta-blocker resulted in one withdrawal in each treatment arm. In MRCOA 1992 , un-blinded physicians made decisions regarding severity of side effects and continuation of therapy; 176 subjects in the beta-blocker group were withdrawn because of bradycardia.

D I S C U S S I O N

Discussion

This systematic review provides the best available evidence for antihypertensive treatment for people with elevated blood pressure who are at least 60 years of age. It is important to appreciate that this represents a group of people with relatively high systolic blood pressures: an average of 172/81 mmHg in the isolated systolic hypertension trials and an average of 182/95 mmHg in the 11 other trials. The reason that the diastolic pressure is lower than expected is because only 6 of these trials ensured the presence of diastolic hypertension, i.e. > 90 mmHg diastolic (ANBP 1981 , EWPHE 1989 , HTN Coop 1974 , Sprackling 1981 , STOP 1991 , VA Coop 1970). In these trials the average diastolic BP was >100 mmHg.

In this population antihypertensive drug treatment was associated with a modest reduction in total mortality, RR 0.90 (0.84 - 0.97). This represents an absolute reduction in deaths of 12, from 116 to 104 events per 1000 participants, over an average duration of 4.5 years, see . However, the 95% CI range from 3 to 19 deaths per 1000 participants, so we cannot be very confident in this result. This absolute reduction is explained by 6 less deaths due to stroke and 6 less deaths due to coronary heart disease. Most importantly when we limited the analysis to people 80 years old and over there was no reduction in total mortality, RR 0.98 (0.87 - 1.10). Thus trials with longer duration of treatment in the very elderly are warranted.

Cardiovascular mortality and morbidity was significantly reduced, RR 0.72 (0.68 - 0.77). This represents an absolute reduction of 43 (35 - 49), from 153 to 110 events per 1000 participants for a mean duration of treatment of 4.5 years, see . This was due to a reduction of 20 cerebrovascular disease mortality and morbidity events as well as 10 coronary heart disease mortality and morbidity events. In the very elderly a similar reduction of 18 cerebrovascular mortality and morbidity events per 1000 participants was present, but there was no significant reduction in coronary heart disease mortality and morbidity.

The magnitude of benefit depends on multiple factors including their baseline risk of cardiovascular complications of hypertension (Gueyffier 1997). People with more cardiovascular risk factors (e.g. diabetes, family history of heart disease, left ventricular hypertrophy, etc.) have greater likelihood of a reduction in cardiovascular events by antihypertensive therapy.

The five-year absolute morbidity and mortality benefit of antihypertensive therapy is greater for older than younger adults (Collins 1990 , Mulrow 1994). Several reasons could explain this greater absolute benefit. First, older people are at higher immediate absolute risk of a cardiovascular event than younger people (Alderman 1981 , Browner 1989 , Alderman 1993). The risk factors include pre-existing cardiovascular disease and systolic hypertension (Applegate 1992 , Mann 1992). Lowering of blood pressure results in similar relative but higher absolute effect in these people at high risk. The subgroup analysis of treatment in the very elderly patients (80 years or older) showed no significant benefit in terms of all cause mortality including cardiovascular, coronary heart disease or cerebrovascular disease mortality. However, a higher absolute risk reduction was observed in cardiovascular mortality and morbidity from 115 to 86 (75 to 100) events per 1000 participants, which was mostly due to a decrease in cerebrovascular mortality and morbidity for a mean duration of 2.0 years, see .

Trials involving older people could have varied systematically from those in younger people. Except for TOMHS 1995 , trials that included younger people were published before 1987(VA Coop 1962 , Wolf 1966 , VA Coop 1970 , Barraclough 1973 , HTN Coop 1974 , USPHS Coop 1977 , VA/NHLBI 1978 , ANBP 1981 , Oslo 1986). Six large trials involving older people were published after 1990 (SHEP 1991 , STOP 1991 , MRCOA 1992 , Syst-Eur 1991 , HYVET P 2003 , HYVET 2008). While first-line beta-blockers and thiazide diuretics were used in most trials, the recent large trials in older people have usually used either lower doses of thiazides or combinations with potassium sparing agents. As a result they may be associated with less toxic adverse effects. The most recent trial in very elderly (HYVET 2008) used indapamide sustained release 1.5 mg or matching placebo. If blood pressure remained above SBP=150 mmHg and DBP=80 mmHg, perindopril 2 mg or 4 mg or matching placebo could be added. Thus, this trial showed a significant reduction in mortality, RR 0.82 (0.69 - 0.99), ARR = 2.2%, NNT= 48 for 2 years, and in total cardiovascular events, RR 0.71 (0.57 - 0.87) with low doses of two antihypertensive drugs. The other trials in the very elderly used higher doses of more antihypertensive drugs and showed a trend towards increased total mortality. These observations suggest that less aggressive treatment is probably a good approach in the very elderly, but this needs to be validated with RCTs testing different approaches to BP control in this patient population.

Numbers of participants who dropped out of trials due to adverse drug effects were often not reported. The three trials that did report this data showed a significant increase in withdrawals due to adverse effects from 65 to 111 events per 1000 participants, absolute increase of 46 (29 - 65) per 1000 patients. Separate data for withdrawals due to adverse effects was not available in the very elderly patients.

Control rates

Control rates provide insight regarding baseline risk of study populations and can explain the differences in outcomes between individual trials. Total mortality rates in the control groups ranged from 3 to 71%. Trials with relatively low rates included ANBP 1981 (3%), HYVET P 2003 (5.2%), Syst-Eur 1991 (6%), SHEP-PS 1986 (6.5%), STOP 1991 (7.7%), and SHEP 1991 (10.2%). Trials with moderate rates included HYVET 2008 (12.3%), MRCOA 1992 (14.2%), HEP 1986 (14.8%), and Kuramoto 1981 (14.9%). Trials with relatively high rates included Carter 1970 (34.6%), EWPHE 1989 (35.1%), and Sprackling 1981 (71%). VA Coop 1970 and HTN Coop 1974 did not report total mortality, but reported the second and third highest event rates (behind Sprackling 1981) in cardiovascular morbidity and mortality (VA Coop 1970 58.1%, HTN Coop 1974 34.3% and Sprackling 1981 83.9%).

The 95% CI of the RR of total mortality for Sprackling 1981 , 1.11 (0.90 to 1.36), did not overlap with the 95% CI of the STOP 1991 trial, 0.57 (0.39 to 0.85). Differences in control rates may in part be due to differing baseline characteristics in recruited subjects. For example, the subjects in Carter 1970 and HTN Coop 1974 were all stroke survivors. Subjects in Sprackling 1981 and Kuramoto 1981 resided in a home for the aged. Subjects in Carter 1970 and VA Coop 1962 were recruited from hospitals (though followed up in clinics) and subjects in EWPHE 1989 were recruited from geriatric hospitals, physician's offices and homes for the aged.

Additional explanations of differing control rates include variations in definitions of trial end-points, cross-over rates and follow-up durations. Although we attempted to standardize outcome definitions as much as possible (see Methods section), truly uniform definitions between trials were not possible. Trials had cross-over rates ranging from 9% to 62% (see Characteristics of included studies) and follow-up durations ranging from 1 to 6 years.

Since most data is based on a small percentage of randomized patients with stroke or MI at baseline, patients with significant competing comorbidity and complicated medical regimens may also have poorer compliance, less benefit, and more adverse effects compared to participants in trials.

Risk of Bias

Risk of bias was assessed using the Cochrane Risk of Bias tool and demonstrated that approximately 40% of trials had evidence of selective reporting bias and approximately 30% of trials did not deal with missing or incomplete outcome data appropriately. In other words, 40% of trials could have censored outcome data for patients after they had had their first event. In addition, in 30% of the trials, when outcome data wasn't available it appeared the assumption was that an event did not occur in that patient. See ; and . The implications are that the available outcome data used in the meta-analyses may be incomplete. It is difficult to determine whether this bias would favour treatment or control. What can be said is that reported event rates are underestimates and the calculated effect sizes for outcomes (other than death as the first event) may be inaccurate.

Limitations and generalizability

The most appropriate way to match expected magnitude of benefits to patients with particular constellations of risk factors is to perform individual patient based meta-analyses (Gueyffier 1997), which was not possible in this review. Moreover, our aggregate results only refer to generally expected benefits for elderly hypertensive patients, and are not tailored specifically to patients with particular risk factors. Our average results refer primarily to a primary prevention population with moderate to severe systolic or systodiastolic hypertension treated with a first-line thiazide. Data for other first-line drugs is insufficient, and the objective of this review was not to compare different first-line drugs, which has been done by other systematic reviews (Psaty 1997 , Wright JM 1999 , Psaty 2003 , Wright JM 2009).

Actual estimates of benefits and harms of treating elderly persons with hypertension derived from trials with highly selected subjects are not readily generalizable to clinical practice. Many patients either would not meet eligibility criteria or, if offered the chance, would not have enrolled in a clinical trial. Strictly speaking, trial results cannot be generalized to such patients. In practice, clinicians are of course willing to offer treatment to patients who may not have been eligible for a trial or who, if eligible, would have refused participation; but we should approach these generalizations with forethought. Without extra care and visits provided in many trials, even our "eligible" patients may be less compliant than trial participants. Patients with significant competing comorbidities and complicated medical regimens may also have poorer compliance, less benefit, and more adverse effects compared to participants in trials. For example in an octagenarian with orthostasis and recurring falls related to antihypertensive therapy, the harms likely exceed benefits. On the other hand, clinicians should not always assume that less benefit would be seen in "real life" clinical settings. A person who is at high immediate risk of suffering a cardiovascular event and does not have other competing illnesses may have a higher benefit-to-harm ratio than the average trial participant.

AUTHORS' CONCLUSIONS

Implications for practice

Antihypertensive treatment of people aged 60 and older with moderate to severe systolic and/or diastolic hypertension reduces total mortality and total cardiovascular morbidity and mortality. The absolute risk reduction in cerebrovascular mortality and morbidity over 4.5 years was greater (2.0% and NNT=50) than for coronary heart disease mortality and morbidity (1.0% with NNT=100). The evidence of benefit pertains mostly to a primary prevention population and first-line treatment with a thiazide. This comprehensive systematic review provides additional evidence in people aged 80 and older where antihypertensive treatment reduced total cardiovascular morbidity and mortality, but not total mortality. In the very elderly the absolute risk reduction in cerebrovascular mortality and morbidity over 2.2 years was 1.8% with NNT=56, but there was no significant reduction in coronary heart disease mortality and morbidity.

Implications for research

Individual patient based meta-analyses of data from existing trials should be used to derive evidence for the treatment of specific subgroups of elderly hypertensive

patients, such as persons with diabetes, functional impairment, recent stroke or persons of African descent. Further long term RCTs are needed to investigate which first-line drug is best in elderly patients and to study different approaches to treatment e.g. an RCT comparing the use of two drugs at low dose (as in the HYVET 2008 trial) with traditional antihypertensive therapy with 3 to 4 drugs in maximal doses.

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NOTES

REFERENCES

References to studies included in this review

ANBP 1981 *{published data only}*

The Australian Therapeutic Trial in Mild Hypertension. Lancet 1980;1:1261-67.

Treatment of mild hypertension in the elderly. A study initiated and administered by the National Heart Foundation of Australia. Med J Aust 1981;2:398-402.

Carter 1970 *{published data only}*

Carter AB. Hypotensive therapy in stroke survivors. Lancet 1970;1:485-89.

EWPHE 1989 *{published data only}*

Amery A, Bixko P, Clement D, Schaepdryver A, Fagard R, Forte J. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly Trial. Lancet 1985;1:1349-54.

An international trial of antihypertensive therapy in elderly patients. Objectives, protocol and organization. Arch Int Pharmacodyn 1985;275:300-34.

O'Malley KO, McCormack P, O'Brien ET. Isolated systolic hypertension: data from the European Working Party on High Blood Pressure in the Elderly. J Hypertens 1988;6:S105-8.

Staessen J, Bulpitt C, Clement D, Leeuw P, Fagard R, Fletcher A. Relation between mortality and treated blood pressure in elderly patients with hypertension: report of the European Working Party on High Blood Pressure in the Elderly. BMJ 1989;298:1552-6.

HEP 1986 *{published data only}*

Coope J, Warrender TS. Randomized trial of treatment of hypertension in elderly patients in primary care. BMJ 1986;293:1145-52.

HTN Coop 1974 *{published data only}*

Effect of antihypertensive treatment on stroke recurrence. JAMA 1974;229:409-18.

HYVET 2008 *{published data only}*

Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Belhani A, Forette F, Rajkumar C, Thijs L, Banya W, Bulpitt C. Treatment of Hypertension in Patients 80 Yearsof Age or Older. New England Journal of Medicine 2008;358:1887-1898.

HYVET P 2003 *{published data only}*

Bulpitt CJ, Beckett NS, Cooke J, Dumiktrascu DL, Gil-Extremera B, Nachev C, Nunes M, Peters R, Staessen JA, Thijs L. Results of the pilot study for the Hypertension in the VeryElderly Trial. Journal of Hypertension 2003;21:2409-2417.

Kuramoto 1981 *{published data only}*

Kuramoto K, Matsushita S, Kuwajima T, Murakami M. Prospective study on the treatment of mild hypertension in the aged. Jpn Heart J 1981;22:75-85.

MRCOA 1992 *{published data only}*

Medical Research Council Trial of Treatment of Hypertension in Older Adults: principal results. BMJ 1992;304:405-412.

SHEP 1991 *{published data only}*

Applegate WB, Pressel S, Wittes J, Luhr J, Shekelle RB, Camel GH. al. Impact of the treatment of isolated systolic hypertension on behavioral variables: results from the Systolic Hypertension in the Elderly Program. Arch Intern Med 1994;154:2154-60.

Hulley SB, Furberg CD, Gurland B, McDonald R, Perry HM, Schnaper HW. Systolic Hypertension in the Elderly Program (SHEP): antihypertensive efficacy of chlorthalidone. Am J Cardiol 1985;56:913-20.

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;265:3255-64.

Rationale and design of a randomized clinical trial on prevention of stroke in isolated systolic hypertension. J Clin Epidemiol 1988;41:1197-1208.

SHEP-PS 1986 *{published data only}*

Black DM, Brand RJ, Greenlick M, Hughes G, Smith J. Compliance to treatment for hypertension in elderly patients: the SHEP pilot study. J Gerentol 1987;42:552-7.

Hulley SB, Furberg CD, Gurland B, McDonald R, Perry HM, Schnaper HW. for the SHEP Research Group. Systolic Hypertension in the Elderly Program (SHEP): antihypertensive efficacy of chlorthalidone. Am J Cardiol 1985;56:913-20.

Perry HM, McDonald RH, Hulley SB, Smith WM, Furberg CD, Greenlick MR. Systolic Hypertension in the Elderly Program, Pilot Study (SHEP-PS): morbidity and mortality experience. J Hypertens 1986;4:S21-3.

Perry HM, Smith WM, McDonald RH, Black D, Cutler JA, Furberg CD. Morbidity and mortality in the Systolic Hypertension in the Elderly Program (SHEP) Pilot Study. Stroke 1989;20:4-13.

Sprackling 1981 *{published data only}*

Sprackling ME, Mitchell JRA, Short AH, Watt G. Blood pressure reduction in the elderly: a randomised controlled trial of methyldopa. BMJ 1981;283:1151-3.

STOP 1991 *{published data only}*

Dahlof B, Lindholm LH, Hansson L, Schersten B, Ekbom T, Wester P-O. Morbidity and mortality in the Swedish Trial in Old Patients With Hypertension (STOP-Hypertension). Lancet 1991;338:1281-5.

Syst-Eur 1991 *{published data only}*

Amery A, Birkenhager W, Bulpitt CJ. Syst-Eur: a multicenter trial on the treatment of isolated systolic hypertension in the elderly; objectives, protocol and organisation. Aging 1991;3:287-302.

Celis H, Yodfat Y, Thijs L, Clement D, Cozic J, Cort P, Forette F, Gregoire M, Heyrman J, Stibbe G, Haute M, Staessen J, Fagard R. Antihypertensive therapy in older patients with isolated systolic hypertension: the Syst-Eur experience in general practice. The Syst-Eur Investigators. Fam Pract 1996;13:138-43.

Girerd X, Amery A, Birkenhager W, Bulpitt C, Cox J, Leeuw P. [SYST-EUR: a multicenter trial of treatment of systolic hypertension in aged subjects. An initial report]. [French] Archives des Maladies du Coeur et des Vaisseaux 1992;85:1243-7.

Slovick D, Staessen J, Bert P, Bulpitt C, Cort P, Fagard R. Nitrendipine in older patients with isolated systolic hypertension: second progress report on the Syst-Eur trial. J Hum Hypertens 1993;7:411-2.

Slovick DI, Amery A, Birkenhager W, Bulpitt CJ, Cox J, Leeuw P. Syst-Eur multicenter trial on the treatment of isolated hypertension in the elderly: first interim report. J Hum Hypertens 1993;7:201-3.

Slovick DI, Amery A, Birkenhager W, Bulpitt CJ, Cox J, Leeuw P. Syst-Eur multicenter trial on the treatment of isolated hypertension in the elderly: first interim report. J Hum Hypertens 1993;7:201-3.

Staessen J, Bert P, Bulpitt C. de Cort P, Fagard R, Fletcher A, et al. Nitrendipine in older patients with isolated systolic hypertension: second progress report on the Syst-Eur trial. J Hum Hypertens 1993;7:265-71.

Staessen JA, Fagard R, Thijs Lutgarde, Celis H, Arabidze GG. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. Lancet 1997;350:757-64.

Staessen JA, Thijs L, Clement D, Davidson C, Fagard R, Lehtonen A, Mancia G, Palatini P, O'Brien ET, Parati G. Ambulatory pressure decreases on long-term placebo treatment in older patients with isolated systolic hypertension. Syst-Eur Investigators. J Hypertens 1994;12:1035-9.

Staessen JA, Thijs L, Mancia G, Parati G, O'Brien ET. Clinical trials with ambulatory blood pressure monitoring: fewer patients needed? Syst-Eur Investigators. Lancet 1994;344:1552-6.

Staessen JA, Thijs L, Mancia G, Parati G, O'Brien ET. Clinical trials with ambulatory blood pressure monitoring: fewer patients needed? Syst-Eur Investigators. Lancet 1994;344:1552-6.

Staessen JA, Tijs L, Bieniaszewski L, O'Brien ET, Palatini P, Davidson C, Dobovisek J, Jaaskivi M, Laks T, Lehtonen A, Vanhanen H, Webster J, Fagard R. Ambulatory monitoring uncorrected for placebo overestimates long-term antihypertensive action. Systolic Hypertension in Europe (SYST-EUR) Trial Investigators. Hypertension 1996;27:414-20.

Thijs L, Dabrowska E, Clement D, Fagard R, Laks T, Mancia G, O'Brien E, Omboni S, Parati G, Staessen J. Diurnal blood pressure profile in older patients with isolated systolic hypertension. The SYST-EUR Investigators. J Hum Hypertens 1995;9:917-24.

VA Coop 1970 *{published data only}*

Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA 1970;213:1143-1152.

** indicates the major publication for the study*

References to studies excluded from this review

ADVANCE 2007 *{published data only}*

Eff ects of a fi xed combination of perindopril and indapamideon macrovascular and microvascular outcomes in patientswith type 2 diabetes mellitus (the ADVANCE trial):a randomised controlled trial.. The Lancet 2007;370:829-840.

ALLHAT 1996 *{published data only}*

Davis BR, Cutler JA, Gordon DJ. Rationale and design for the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Am J Hypertens 1996;9:342-60.

Barraclough 1973 *{published data only}*

Barraclough M, Bainton D, Cochrane AL. Control of moderately raised blood pressure: report of a cooperative randomized controlled trial. BMJ 1973;3:434-6.

BMJ 1973 *{published data only}*

Anonymous . Control of moderately raised blood pressure. Report of a co-operative randomized controlled trial. Br Med J 1973;3:434-6.

CASTEL 1994 *{published data only}*

Casiglia E, Spolaore P, Mazza A, Ginocchio G, Colangeli G, Onesto C. Effect of two different therapeutic approaches on total and cardiovascular mortality in a Cardiovascular Study in the Elderly (CASTEL). Jpn Heart J 1994;35:589-600.

Casiglia E, Spolaore P, Mormino P, Maschio O, Colangeli G, Celegon L. The CASTEL project (CArdiovascular STudy in the ELderly): protocol, study design, and preliminary results of the initial survey. Cardiologia 1991;36:569-76.

GLANT 1995 *{published data only}*

A 12-month comparison of ACE inhibitor and CA antagonist therapy in mild to moderate essential hypertension - the GLANT Study. Hypertens Res 1995;18:235-44.

HAPPHY 1987 *{published data only}*

Wilhelmsen L, Berglund G, Elmfeldt D, Fitzsimons T, Holzgreve H, Hosie J, Hornkvist PE, Pennert K, Tuomilehto J, Wedel H. Beta-blockers versus diuretics in hypertensive men: main results from the HAPPHY trial. J Hypertens 1987;5:561-572.

HDFP 1982 *{published data only}*

Curb JD, Borhani NO, Schnaper H, Kass E, Entwisle G, Williams W, Berman R. Detection and treatment of hypertension in older individuals.. Am J Epidemiol 1985;121:371-376.

Five-year findings of the Hypertension Detection and Follow-up Program: III. Reduction in stroke incidence among persons with high blood pressure. JAMA 1982;247:633-8.

Five-year findings of the Hypertension Detection and Follow-up Program: reduction in mortality in persons with high blood pressure, including mild hypertension. JAMA 1979;242:2562-71.

The effect of treatment on mortality in "mild" hypertension: results of the Hypertension Detection and Follow-up Program. New England Journal of Medicine 1982;307:976-80.

Five-year findings of the Hypertension Detection and Follow-up Program: II. Mortality by race-sex and age.. JAMA 1979;242:2572-7.

Maxwell MH, Ford CE. Cardiovascular morbidity and mortality in HDFP patients 50-69 years old at entry. J Cardiovasc Pharmacol 1985;7:S5-9.

HOT 1995 *{published data only}*

Hansson L, Zanchetti A. The Hypertension Optimal Treatment (HOT) Study: 12-month data on blood pressure and tolerability. With special reference to age and gender. Blood Pressure 1995;4:313-9.

HYVET-Cog 2008 *{published data only}*

Peters R, Beckett N, Forette F, Tuomilehto J, Clarke R, Ritchie C, Waldman A, Walton I, Poulter R, Ma S, Comsa M, Burch L, Fletcher A, Bulpitt C. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. Lancet Neurology 2008;7:683-689.

IPPPSH 1985 *{published data only}*

Cardiovascular risk and risk factors in a randomized trial of treatment based on the beta-blocker oxprenolol: the International Prospective Primary Prevention Study in Hypertension (IPPPSH). J Hypertens 1985;3:379-92.

Jikei 2007 *{published data only}*

Mochizuki S, Dahlof B, Shimizu M, Ikewaki K, Yoshikawa M, Taniguchi I, Ohta M, Yamada T, Ogawa K, Kanae K, Kawai M, Seki S, Okazaki F, Taniguchi M, Yoshida S, Tajima N. Valsartan in a Japanese population with hypertensionand other cardiovascular disease (Jikei Heart Study):a randomised, open-label, blinded endpointmorbidity-mortality study. The Lancet 2007;369:1431-1439.

Kuramoto 1994 *{published data only}*

Kuramoto K. Treatment of elderly hypertensives in Japan: National Intervention Cooperative Study in Elderly Hypertensives. The National Intervention Cooperative Study Group. J Hypertens Suppl 1994;12:S35-40.

MAPHY 1988 *{published data only}*

Wikstrand J, Warnold I, Olsson G, Tuomilehto J, Elmfeldt D, Berglund G. Primary prevention with metoprolol in patients with hypertension. Mortality results from the MAPHY study. JAMA 1988;259:1976-82.

Materson 1993 *{published data only}*

Materson BJ, Reda DJ, Cushman WC. Department of Veterans Affairs single-drug therapy of hypertension study. Revised figures and new data. Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Am J Hypertens 1995;8:189-92.

Materson BJ, Reda DJ, Cushman WC, Massie BM, Freis ED, Kochar MS. Single-drug therapy for hypertension in men: a comparison of six antihypertensive agents with placebo. N Engl J Med 1993;328:914-21.

MIDAS 1996 *{published data only}*

Borhani NO, Mercuri M, Borhani PA, Buckalew VM, Canossa-Terris M, Carr AA. Final outcome results of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS). JAMA 1996;276:785-91.

Morgan 1980 *{published data only}*

Morgan TO, Adams WR, Hodgson M, Gibberd RW. Failure of therapy to improve prognosis in elderly males with hypertension. Med J Aust 1980;2:27-31.

MRC 1985 *{published data only}*

MRC trial of treatment of mild hypertension: principal results. Br Med J (Clin Res Ed) 1985;291:97-104.

Oslo 1986 *{published data only}*

Leren P, Helgeland A. Oslo Hypertension Study. Drugs 1986;31:41-5.

PATS 1995 *{published data only}*

Post-stroke antihypertensive treatment study. A preliminary result. Chinese Medical Journal 1995;108:710-7.

SCOPE 2003 *{published data only}*

Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, Trenkwalder P, Zanchetti A. The Study on Cognition and Prognosis in the Elderly(SCOPE): principal results of a randomized double-blindintervention trial. Journal of Hypertension 2003;21:875-886.

SHELL 1994 *{published data only}*

Malacco E, Gnemmi AE, Romagnoli A, Coppini A. Systolic hypertension in the elderly: long-term lacidipine treatment. Objective, protocol, and organization. SHELL Study Group. J Cardiovasc Pharmacology 1994;23:S6206-.

STONE 1996 *{published data only}*

Gong L, Zwang W, Zhu Y. Shanghai Trial of Nifedipine in the Elderly (STONE) Study. J Hypertens 1996;14:1237-46.

STOP-2 1993 *{published data only}*

Dahlof B, Hansson L, Lindholm LH. STOP-Hypertension-2: A prospective intervention trial of "newer" versus "older" treatment alternatives in old patients with hypertension. Blood Pressure 1993;2:136-41.

Syst-China 1993 *{published data only}*

Anonymous . [Systolic hypertension in the elderly: Chinese trial (Syst-China). Interim report]. [Chinese] Chung-Hua Hsin Hsueh Kuan Ping Tsa Chih [Chinese Journal of Cardiology] 1992;20:270-5,323.

Anonymous . [Systolic hypertension in the elderly: Chinese trial (Syst-China)--second interim report]. [Chinese] Chung-Hua Hsin Hsueh Kuan Ping Tsa Chih [Chinese Journal of Cardiology] 1993;21:135-7,185.

TOMHS 1995 *{published data only}*

Elmer PJ, Grimm R, Laing B, Grandits G, Svedsen K, Heel N. Lifestyle intervention: results of the Treatment of Mild Hypertension Study (TOMHS). Prev Med 1995;24:378-88.

The Treatment of Mild Hypertension Study: a randomized, placebo-controlled trial of a nutritional-hygienic regimen along with various drug monotherapies. Arch Intern Med 1991;151:1413-23.

USPHS Coop 1977 *{published data only}*

Treatment of mild hypertension: results of a ten year intervention trial. Circ Res 1977;40:98-105.

VA Coop 1962 *{published data only}*

A double-blind control study of antihypertensive agents. I. Comparative effect of reserpine, reserpine and hydralazine, and three ganglionic blocking agents, clorisondamine, mecamylamine, and pentolinium tartrate. Arch Intern Med 1960;106:133-48.

A double-blind control study of antihypertensive agents. II. Further report on the comparative effectiveness of reserpine, reserpine and hydralazine, and three ganglionic blocking agents, clorisondamine, mecamylamine, and pentolinium tartrate. Arch Intern Med 1962;110:222-9.

A double-blind control study of antihypertensive agents. III. Chlorothiazide alone and in combination with other agents: preliminary results. Arch Intern Med 1962;110:230-5.

VA/NHLBI 1978 *{published data only}*

Lung . Evaluation of drug treatment in mild hypertension: VA-NHLBI feasibility trial. Ann NY Acad Sci 1978;304:267-288.

White 1995 *{published data only}*

White WB, Stimpel M. Long-term safety and efficacy of moexipril alone and in combination with hydrochlorothiazide in elderly patients with hypertension. J Human Hypertens 1995;9:879-84.

Wolf 1966 *{published data only}*

Wolf FW, Lindeman RD. Effects of treatment in hypertension. Results of a controlled study. J Chronic Dis 1966;19:227-40.

Additional references

Alderman 1981

Alderman MH, Madhavan S. Management of the hypertensive patient: a continuing dilemma. Hypertension 1981;3:192-7.

Alderman 1993

Alderman MH. Blood pressure management: Individualized treatment based on absolute risk and the potential for benefit. Ann Intern Med 1993;119:329-35.

Applegate 1992

Applegate WB, Miller ST, Elam JT, Cushman WC, Derwi D, Brewer A, Graney M J. Nonpharmacologic intervention to reduce blood pressure in older patients with mild hypertension. Arch-Intern-Med 1992;152:1162-6.

Browner 1989

Browner WS, Hulley SB. Implications of hypertension trials: effect of risk status on treatment criteria. Hypertension 1989;13:51-6.

Celis 1993

Celis H, Fagard R, Staessen J, Thijs L, Amery A. The older hypertensive: Assessment and treatment. Netherlands Journal of Medicine 1993;43:S66-77.

Collins 1990

Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, Godwin J, Qizilbash N, Taylor JO, Hennekens CH. 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;335:827-38.

Davidson 1987

Davidson RA, Caranasos GJ. Should the elderly hypertensive be treated? Evidence from clinical trials. Arch Intern Med 1987;147:1933-37.

Ebrahim 2006

Ebrahim S, Beswick A, Burke M, Davey Smith G. Multiple risk factor interventions for primary prevention of coronary heart disease. Cochrane Database of Systematic Reviews 2006:-.

Gueyffier 1997

Gueyffier F, Boutitie F, Boissel JP, Pocock S, Coope J, Cutler J. Effect of antihypertensive drug treatment on cardiovascular outcomes in women and men. A meta-analysis of individual patient data from randomized, controlled trials. The INDANA Investigators. Ann Intern Med 1997;126:761-7.

Gueyffier F 1999

Gueyffier F, Bulpitt C, Boissel . Antihypertensive drugs in very old people: a subgroup meta-analysis of randomized controlled trials. Lancet 1999;353:793-796.

Insua 1994

Insua JT, Sacks HS, Lau TS, Lau J, Reitman D, Pagano D, Chalmers T. Drug treatment of hypertension in the elderly: A meta-analysis. Ann Intern Med 1994;121:355-62.

Ioannidis 1997

Ioannidis JPA, Lau J. The impact of high-risk patients on the results of clinical trials. J Clin Epidemiol 1997;50:1089-98.

Leonetti 1992

Leonetti G, Cuspidi C, Fastidio M, Lonati L, Chianca R. Arterial hypertension as a risk factor in the elderly and its treatment. Journal of Hypertension 1992;10:S3-7.

MacMahon 1993

MacMahon S, Rogers A. The effects of blood pressure reduction in older patients: an overview of five randomized controlled trials in elderly hypertensives. Clin Exper Hypertension 1993;15:967-78.

Mann 1992

Mann SJ. Systolic hypertension in the elderly. Arch Intern Med 1992;152:1977-84.

Musini VM 2008

Musini VM, Tejani A, Bassett K, Wright JM. Treatment of elevated blood pressure in the elderly. Less is better. Therapeutics Initiative (www.ti.ubc.ca) ;Therapeutics Letter 71:1-2.

Pearce 1995

Pearce KA, Furberg CD, Rushing J. Does antihypertensive treatment of the elderly prevent cardiovascular events or prolong life?. Arch Fam Med 1995;4:943-50.

Psaty 1997

Psaty BM. Smith NL. Siscovick DS. Koepsell TD. 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;289:2534-2544.

Schmid 1998

Schmid CH, Lau J, McIntosh MW, Cappelleri JC. An empirical study of the effect of the control rate as a predictor of treatment efficacy in meta-analysis of clinical trials. Statistics in Medicine 1998;17:1923-1942.

Staessen 1988

Staessen J, Fagard R, Hoof R, Amery A. Mortality in various intervention trials in elderly hypertensive patients: A review. European Heart Journal 1988;9:215-22.

Staessen 1990a

Staessen J, Fagard R, Hoof R, Amery A. Intervention trials in elderly hypertensive patients: a review. Journal of Hypertension 1990;8:S63-7.

Staessen 1990b

Staessen J, Amery A, Fagard R. Isolated systolic hypertension in the elderly. Journal of Hypertension 1990;8:393-405.

Thijs 1992

Thijs L, Fagard R, Lijnen P, Staessen J, Hoof R, Amery A. A meta-analysis of outcome trials in elderly hypertensives. Journal of Hypertension 1992;10:1103-9.

Thijs 1994

Thijs L, Fagard R, Lijnen P, Staessen J, Hoof R, Amery A. Why is antihypertensive drug therapy needed in elderly patients with systodiastolic hypertension?. Journal of Hypertension 1994;12:S25-34.

Wright JM 1999

Wright JM, Lee Cheng-Han, Chambers KG. Systematic review of antihypertensive therapies: Does the evidence assist in choosing a first-line drug?. Canadian Medical Association Journal 1999;161:25-32.

Wright JM 2009

Wright JM. First-line drugs for hypertension. Cochrane Database of Systematic Reviews 2009:-.

GRAPHS

Graphs and Tables

To view a graph or table, click on the outcome title of the summary table below.

Antihypertensive drug therapy vs control in elderly 60 years or older

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
1 Total mortality	12	23119	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.84, 0.97]
1.1 Elderly 60 years or older	12	23119	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.84, 0.97]
2 Cardiovascular mortality and morbidity	13	23094	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.68, 0.77]
2.1 Elderly 60 years or older	13	23094	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.68, 0.77]
3 Withdrawal due to adverse effects	3	6914	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [1.45, 2.00]

Antihypertensive drug therapy vs control in very elderly 80 years or older

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
1 Total mortality	8	6701	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.87, 1.10]
1.1 Very elderly 80 years or older	8	6701	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.87, 1.10]
2 Cardiovascular mortality and morbidity	7	6546	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.65, 0.87]
2.1 Very elderly 80 years or older	7	6546	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.65, 0.87]

Antihypertensive drug therapy vs control in elderly with ISH

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
1 Total mortality	3	9982	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.77, 1.01]
1.1 Elderly 60 years or older	3	9982	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.77, 1.01]
2 Cardiovascular morbidity and mortality	3	9982	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.61, 0.75]
2.1 Elderly 60 years or older	3	9982	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.61, 0.75]
3 Withdrawal due to adverse effects 60 years or older	3	6914	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [1.45, 2.00]

COVER SHEET

Pharmacotherapy for hypertension in the elderly

Reviewer(s)	Musini Vijaya M, Tejani Aaron M, Bassett Ken, Wright James M
Contribution of Reviewer(s)	
Issue protocol first published	1998 issue 3
Issue review first published	1998 issue 3
Date of last minor amendment	Information not supplied by reviewer
Date of last substantive amendment	Information not supplied by reviewer
Most recent changes	
Date new studies sought but none found	Information not supplied by reviewer
Date new studies found but not yet included / excluded	Information not supplied by reviewer
Date new studies found and included / excluded	Information not supplied by reviewer
Date reviewers' conclusions section amended	Information not supplied by reviewer
Contact address	Musini 2176 Health Science Mall 3935 Kincaid Street Vancouver Burnaby BC BC Canada Canada V6T 1Z3 V5G 2X6 Telephone: Facsimile: E-mail: vijaya@ti.ubc.ca
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COMMENTS AND CRITICISMS

Comment on the conclusion

Summary of comments and criticisms

While reading your interesting review in the Cochrane Library: "Pharmacotherapy for hypertension in the elderly", we were particularly interested in a statement made in the Main results of the abstract:" The average prevalence of cardiovascular risk factors, cardiovascular disease, and competing co-morbid diseases was lower among trial participants than the general population of hypertensive elderly persons." We would very much like to know how you came to that conclusion. After carefully reading the full review, we were not able to find this statement mentioned in any other part of the review. Could you please provide how you validated this statement and what references were used to validate this statement?

Reviewer's reply

Contributors to comment

Saba T.A. and Berger Ch.
Fifth year Pharmacy Students
Department of pharmacology
University of Lausanne
Switzerland
We certify that we have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of our criticisms.

Conclusions are flawed, 28 October 2008

Summary of comments and criticisms

As stated in the title and objectives: The purpose of this SR was to provide a comprehensive overview of trial evidence regarding benefits of "anti-hypertensive drug" therapy in elders.
This systematic review can be criticized mainly because it includes the HDFP trial (in which patients were randomized to two different treatment strategies, i.e. stepped care vs. referred care. In other words, in this trial not only the type of pharmacological agents were different in both groups, but also non-pharmacological interventions. Thus, it is not possible to be certain if the difference in outcomes was due to pharmacological or to non-pharmacological interventions) and CASTEL trial (similar design as that of HDFP) and pooled these trials along with true placebo control trials. Thus, when calculating total mortality, the weight given to those two trials in combination is even greater than that given to the biggest placebo-control trial, SHEP trial. If those two trials were removed the benefit disappears. Therefore, the conclusions of this

systematic review are flawed.

Reviewer's reply

Contributors to comment

Marco Perez
Occupation MD/research
Department of Anesthesiology, Pharmacology & Therapeutics
University of British Columbia
Vancouver, BC Canada
I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

KEYWORDS

Aged; Aged, 80 and over; Humans; Middle Aged; Age Factors ; Antihypertensive Agents [adverse effects] [*therapeutic use] ; Cause of Death ; Hypertension [*drug therapy] [mortality] ; Myocardial Infarction [prevention & control] ; Randomized Controlled Trials as Topic ; Stroke [prevention & control] ; Withholding Treatment

HISTORY

History
Protocol first published: Issue 3, 1998
Review first published: Issue 3, 1998

Date	Event	Description
11 August 2009	Feedback has been incorporated	Excluded HDFP trial since it is a multi-interventional study.
11 August 2009	New citation required and conclusions have changed	substantive update, authors and conclusions have changed
28 October 2008	Feedback has been incorporated	New feedback received 28 October 2008.
13 August 2008	Amended	Converted to new review format.
5 June 2006	Amended	Minor update.
17 November 2004	Feedback has been incorporated	Feedback added.

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