

Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger people: meta-analysis of randomised trials

Blood Pressure Lowering Treatment Trialists' Collaboration

EDITORIAL by Staessen and colleagues

Correspondence to: F Turnbull, Blood Pressure Lowering Treatment Trialists' Collaboration, George Institute for International Health, University of Sydney, PO Box M201, Sydney, NSW 2050, Australia
fturnbull@george.org.au

BMJ 2008;336:1121-3
doi:10.1136/bmj.39548.738368.BE

ABSTRACT

Objective To quantify the relative risk reductions achieved with different regimens to lower blood pressure in younger and older adults.

Design Meta-analyses and meta-regression analyses used to compare the effects on the primary outcome between two age groups (<65 v ≥65 years). Evidence for an interaction between age and the effects of treatment sought by fitting age as a continuous variable and estimating overall effects across trials.

Main outcome measures Primary outcome: total major cardiovascular events.

Results 31 trials, with 190 606 participants, were included. The meta-analyses showed no clear difference between age groups in the effects of lowering blood pressure or any difference between the effects of the drug classes on major cardiovascular events (all $P \geq 0.24$). Neither was there any significant interaction between age and treatment when age was fitted as a continuous variable (all $P > 0.09$). The meta-regressions also showed no difference in effects between the two age groups for the outcome of major cardiovascular events (<65 v ≥65; $P = 0.38$).

Conclusions Reduction of blood pressure produces benefits in younger (<65 years) and older (≥65 years) adults, with no strong evidence that protection against major vascular events afforded by different drug classes varies substantially with age.

INTRODUCTION

Observational studies have shown that blood pressure levels are strongly and directly related to the relative risks of stroke and heart disease¹ but that the strength of the association declines with increasing age.² A recent large overview found that for each 20 mm Hg lower usual systolic blood pressure, the risk of stroke was 33% lower in those aged 80-89 but 62% lower in those aged 50-59.³ While many trials with broad entry criteria for age have investigated the effects of lowering blood pressure on major vascular events, consistently larger reductions in relative risk have not been reported for younger participants. Likewise, there is a paucity of evidence about the effects of different drug classes in older compared with younger patients. The Blood Pressure Lowering Treatment Trialists' Collaboration was established to perform a series of overviews of trials investigating the effects of drugs to lower blood pressure on cardiovascular mortality and morbidity. We compared the proportionate risk reductions

achieved with different classes of drugs in younger and older adults.

METHODS

Trials included—Trials were eligible for inclusion if they randomised patients between a drug to lower blood pressure and control (placebo or less intensive blood pressure treatment) or randomised patients between regimens based on different classes of drug to lower blood pressure. We included in our analyses trials for which data had been obtained by September 2006.

Age groups—The age groups were <65 and ≥65 years at the time of entry into the trial, henceforth referred to as “younger” and “older” adults.

Outcomes—Our primary outcome was total major cardiovascular events, comprising stroke (non-fatal stroke or death from cerebrovascular disease), coronary heart disease (non-fatal myocardial infarction or death from coronary heart disease including sudden death), and heart failure (causing death or resulting in admission to hospital). Secondary outcomes were stroke, coronary heart disease, heart failure, cardiovascular death, and total mortality.

Comparisons—The seven comparisons of treatment were: (a) angiotensin converting enzyme inhibitor versus placebo, (b) calcium antagonist versus placebo, (c) more intensive versus less intensive regimens to lower blood pressure, (d) angiotensin receptor blocker versus control regimen, (e) angiotensin converting enzyme inhibitor versus diuretics/β blockers, (f) calcium antagonist versus diuretics/β blockers, and (g) angiotensin converting enzyme inhibitor versus calcium antagonists. Additional comparisons examining the separate effects of diuretics and β blockers in different age groups were (a) angiotensin converting enzyme inhibitor or calcium antagonist versus β blockers and (b) angiotensin converting enzyme inhibitor or calcium antagonist versus diuretics.

Statistical analyses—We calculated the reduction in blood pressure in each trial arm and the mean difference in blood pressure between randomised groups. We performed three sets of analyses to explore the impact of age on the proportional risk reduction achieved with lowering blood pressure. Firstly, we carried out meta-analyses of subgroups of participants defined according to age for each trial and each outcome and estimated the relative risk and its variance separately for each of the two age groups according to the principle of intention to treat. Secondly, we investigated interactions between

This article is an abridged version of a paper that was published on bmj.com. Cite this article as: *BMJ* 2008, doi: 10.1136/bmj.39548.738368.BE

treatment to lower blood pressure and age taken as a continuous variable by fitting regression models including treatment, continuous age, and their interaction. Thirdly, we carried out meta-regression analyses to explore the association between the difference in systolic blood pressure at follow-up between randomised groups and the log relative risk for cardiovascular events in each age group.

RESULTS

Characteristics of trials and patients included

Of the 37 eligible trials,^{w1-w38} we included 31 (190 606 individuals) in these analyses (see table A on bmj.com). For the six remaining trials^{w33-w38} we could not extract data according to criteria specified in the original study protocol.⁴ There were 96 466 individuals aged <65 and 94 140 aged ≥65 at baseline who contributed to the primary analyses. The mean age in the two groups was 57 and 72 and the proportion of men was 58% and 51%, respectively. Mean baseline blood pressure was higher in the older age groups, as was the proportion of primary outcome events that comprised stroke.

Meta-analyses of effects of treatments in different age groups

For the primary outcome, total major cardiovascular events, in the trials that examined blood pressure lowering regimens compared with placebo or less active control, there was no evidence of any difference in reductions in relative risk in different age groups (all $P>0.2$ for heterogeneity). Likewise, in the overviews of trials comparing blood pressure lowering regimens based on different drug classes there was no difference in the proportional reductions in total major cardiovascular events observed between age groups for any comparison (all $P>0.3$ for heterogeneity). While there was some variation in the reductions in blood pressure with the randomised treatments between age groups, there was no systematic pattern. Among the 35 comparisons between age groups made for the secondary outcomes there were two with $P\leq 0.05$, and these are likely to have arisen by chance.

We used data from eight trials^{w1 w5 w6 w10 w27-w29 w31} in subsidiary analyses to examine the separate effects of regimens based on β blockers and on diuretics compared with other drug classes according to patients' age. In these analyses, there was no evidence of a difference in the proportional risk reduction for major cardiovascular events between younger and older adults for either comparison (all $P>0.38$).

Effects of age on blood pressure lowering with age fitted as continuous variable

We found no evidence of an interaction between age and the effects of treatment on the primary outcome of major cardiovascular events for any blood pressure lowering treatments compared with control (all $P>0.09$). The same was true for the comparisons of different active agents (all $P>0.2$). For the secondary

outcomes there was one significant interaction ($P=0.02$) among the 30 analyses, and this is most likely to have arisen by chance.

Meta-regressions of effects of blood pressure lowering in different age groups

There was no difference in the risk reduction achieved per unit reduction in blood pressure for individuals aged <65 compared with ≥65 for the primary outcome of total major cardiovascular events ($P=0.38$) nor for any of the secondary outcomes (all $P\geq 0.18$).

DISCUSSION

Principal findings

These analyses provide support for the use of drugs to lower blood pressure in older and younger adults, with no strong evidence for the selective use of specific classes of drug according to age. Factors such as tolerability and cost are probably reasonable bases for choice of drug so long as effective blood pressure reduction is achieved.⁵⁻⁷ In particular, for these age groups, there was no evidence of differences between the effects of β blockers and other classes of drugs in older compared with younger adults for any outcome studied, and the same was true for all other drug comparisons.

Findings in context of observational studies

We might expect variation in the effect of lowering blood pressure because observational data have shown less strong proportional associations of blood pressure levels with risk in older compared with younger adults.³ In our analyses there were some comparisons that showed evidence of different effects of blood pressure lowering between age groups. It is important, however, that the "statistically significant" subsidiary analyses are interpreted in light of their post hoc nature, and the multiple comparisons made. Our results do not completely exclude the possibility of differences in the proportional effects of blood pressure lowering regimens between age groups but they do suggest that any such differences are likely to be small.

Clinical implications

As the magnitude of the proportional risk reduction achieved with blood pressure lowering does not seem to decline with age, our findings provide strong support for the use of blood pressure lowering in elderly people. Among the older age group there was, in almost every analysis and for almost every outcome, an estimate of effect suggesting benefit from blood pressure lowering, and in no case was there evidence of harm. These data also provide reassurance that current approaches to the use of blood pressure lowering treatments that assume constant proportional risk reductions across age groups⁵⁻⁹ are appropriate.³

WHAT IS ALREADY KNOWN ON THIS TOPIC

In observational studies the proportional reductions in the risks of vascular disease associated with lower blood pressure levels decline with increasing age, suggesting that the relative effects of blood pressure lowering drugs might be smaller among elderly people

Some blood pressure management guidelines recommend specific classes of blood pressure lowering treatment for particular age groups

WHAT THIS STUDY ADDS

Blood pressure reduction produces similar proportional reductions in the risks of vascular events in younger (<65 years) and older (≥65 years) adults

The absolute benefits of treatment are likely to be particularly large among older individuals because of their higher average risk

There was no clear evidence to support recommendations for particular drug classes in older or younger adults

Strengths and weaknesses

Our analyses included thousands of major cardiovascular events and provided reasonably precise estimates of the effects of the different regimens in older and younger adults for most outcomes. They are, however, subject to several limitations. Firstly, the difference in mean age between the older and younger participants was not large—only about 15 years. It is possible that these overviews could have failed to detect real differences in the effectiveness of blood pressure lowering between age groups. That said, the analyses with age fitted as a continuous variable had much better statistical power to detect interactions between age and treatment to lower blood pressure and provide reassurance that moderate or large effects have not been missed. Secondly, because most patients in the trials fell within a fairly limited age range, the analyses were unable to define the effects of blood pressure lowering agents in very elderly people and younger age groups.¹⁰ Thirdly, although there was reasonable comparability in the baseline characteristics of younger and older patients it is possible that different levels of baseline blood pressure, the proportion of men, and possibly other comorbidities might have had an effect on the potential to detect differences between the age groups. Fourthly, the overviews defined only the short to medium term effects of the regimens studied. Fifthly, the ability of these analyses to detect differences between regimens would have been diminished by incomplete adherence to randomised treatments and the extensive use of add-on therapies. Similarly, the a priori definition of a “conventional group” that combines two different drug classes (diuretics and β blockers) represents an additional challenge, although subsidiary analyses were not able to detect differences when β blockers and diuretics were considered separately. Sixthly, data defined by the prespecified criteria were not available for all eligible trials, but limited subsidiary analyses including

published data from those studies did not change the overall study conclusions. Finally, the primary analyses were based on the composite outcome of major cardiovascular events, and this outcome might underestimate any real difference in the proportional effects of blood pressure lowering between age groups. The reason for this is that the composition of major cardiovascular events varies between age groups.

Conclusions

Our results confirm the benefits of effective control of blood pressure in older and younger adults. They also provide substantial reassurance that, within the age range studied, the benefits of regimens to lower blood pressure based on different drug classes are largely comparable across age groups, although there is a relative paucity of data for those under 50 and over 80.

Details of members of the Blood Pressure Lowering Treatment Trialists' Collaboration, the Collaboration Coordinating Centre, and the writing committee are on bmj.com.

Contributors: See bmj.com.

Funding: National Health and Medical Research Council of Australia. B Neal was supported by a fellowship awarded by the National Heart Foundation of Australia. T Ninomiya was supported by a fellowship awarded by the Banyu Life Science Foundation and by an International Society of Hypertension visiting postdoctoral fellowship awarded by the Foundation for High Blood Pressure Research Council of Australia. V Perkovic was supported by a postdoctoral fellowship awarded by the National Heart Foundation of Australia.

Competing interests: Of the members of the writing committee, FT, BN, TN, HA, CB, JC, VP, MW, and SM have received travel expenses, payment for speaking at meetings, or research funding from one or more agencies that sponsored trials included in this collaboration.

Ethical approval: Not required.

Provenance and peer review: Not commissioned; externally peer reviewed.

- 1 MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, et al. Blood pressure, stroke, and coronary heart disease. Part 1. Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990;335:765-74.
- 2 Prospective Studies Collaboration. Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. *Lancet* 1995;346:1647-53.
- 3 Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903-13.
- 4 World Health Organization-International Society of Hypertension Blood Pressure Lowering Treatment Trialists' Collaboration. Protocol for prospective collaborative overviews of major randomized trials of blood-pressure lowering treatments. *J Hypertens* 1998;16:127-37.
- 5 Chobanian A, Bakris G, Black H, Cushman W, Green L, Izzo J, et al. The seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure. The JNC 7 report. *JAMA* 2003;289:2560-72.
- 6 Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). 2007 guidelines for the management of arterial hypertension. *J Hypertens* 2007;25:1105-87.
- 7 World Health Organization. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens* 2003;21:1983-92.
- 8 Canadian Hypertension Education Program. 2007 guidelines for the management of arterial hypertension. *Can J Cardiol* 2007;23:539-50.
- 9 National Collaborating Centre for Chronic Conditions. *Hypertension: management in adults in primary care: pharmacological update*. London: Royal College of Physicians, 2006.
- 10 Brown M, Cruickshank J, Dominiczak A, MacGregor G, Poulter N, Russell G. Better blood pressure control: how to combine drugs. *J Hum Hypertens* 2003;17:81-6.

Accepted: 4 April 2008