Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: a systematic review and meta-analysis

CRD summary
This review concluded that intensive blood pressure lowering regimes provided greater vascular protection than standard regimes but had no effect on death or serious adverse events. Most participants had additional risk factors and caution should be used in generalising results to those with hypertension alone. Because of this, and wide variations in target levels, the conclusions should be treated with caution.

Authors' objectives
To assess the risks and benefits of different intensities of blood pressure lowering medications.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched to July 2011. Search terms were reported. No language restrictions were applied. Reference lists of identified papers and reviews and ClinicalTrials.gov were checked

Study selection
Randomised controlled trials (RCTs) with at least six months follow-up that assessed pharmacological blood pressure lowering agents in people with hypertension or high vascular/renal risk or both and compared more versus less intensive blood pressure targets were eligible for inclusion. The primary outcome of interest was a composite of major cardiovascular events (myocardial infarction, stroke, heart failure and cardiovascular death). Secondary outcomes were myocardial infarction, stroke, heart failure, cardiovascular death, all-cause mortality, end stage kidney disease and adverse outcomes. In studies on people with diabetes, albuminuria (new onset of micro- or macro-albuminuria or progression to macro-albuminuria) and retinopathy (progression of two or more steps) were also reported.

One of the included studies was on children (mean age 11.5 years; with chronic kidney disease and hypertension). Others were on adults (mean ages from 41 to 76 years). Between 25.7 and 62.5% of the participants were women. Some studies were on people with diabetes, others chronic kidney disease and in most studies people had hypertension. Two studies were on people with diabetes without hypertension. In the studies in adults mean baseline blood pressures ranged from 131/80 to 172/105mmHg. Target blood pressures varied substantially: in the more intensive treatment groups diastolic 65 to 85mmHg, systolic less than 120 to less than 150mmHg or mean blood pressure less than 92mmHg; and those in the less intensive group diastolic less than 80 to 95mmHg, systolic less than 140 to less than 180mmHg or mean blood pressure less than 107mmHg. Study reports dated from 1995 to 2010.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
Quality was assessed according to items that included the Cochrane Collaboration risk of bias tool. These included methods of randomisation, concealment of allocation, similarity of baseline characteristics, description of eligibility criteria, completeness of follow-up and intention-to-treat analysis.

Two reviewers independently assessed quality.

Data extraction
Data were extracted in order to calculate risk ratio (RR) and 95% confidence intervals (CI) for dichotomous data and mean differences and 95% confidence intervals for continuous data.

Two reviewers independently extracted data. Disagreements were resolved by a third reviewer.

Methods of synthesis
Pooled risk ratio and mean differences, each with 95% confidence intervals, were calculated using a random-effects
model. Heterogeneity was assessed using $I^2$ statistic. Subgroup analyses investigated the possible effects of study characteristics (numbers of participants, cardiovascular event rates, age, diabetes, blood pressure target and blood pressure level at baseline). Meta-regression was used to investigate possible heterogeneity (numbers of participants, cardiovascular event rates, follow-up, age and baseline systolic blood pressure).

Publication bias was assessed using funnel plots and Egger's test.

**Results of the review**

Fifteen RCTs (37,348 participants) were included. One study included 18,790 participants, others ranged from 75 to 4,733. Mean follow-up ranged from 1.6 to 12.2 years. At follow-up the weighted mean difference in blood pressure between the more intensive and less intensive targets was 7.5 mmHg for systolic and 4.5 mmHg for diastolic blood pressure.

Sequence generation was adequate in 12 studies and unclear in two. Allocation concealment was adequate in 11 studies and unclear in three. Investigators were unblinded to treatment allocation in all studies. Participants were blinded in only three studies and outcome assessors were blinded in nine studies; blinding was unclear in five studies. Eight studies addressed incomplete outcome data and this was unclear in six studies. One study was missed from the quality assessment table. Tests did not show evidence of publication bias.

Compared to less intensive blood pressure lowering targets, more intensive targets reduced the risk of major cardiovascular events (RR 0.89, 95% CI 0.79 to 0.99; $I^2=28.2$%; 10 trials), stroke (RR 0.76, 95% CI 0.63 to 0.92; $I^2=23.2$%; 10 trials), end stage kidney failure (RR 0.89, 95% CI 0.82 to 0.97; $I^2=0$%; eight trials) and myocardial infarction (RR 0.87, 95% CI 0.75 to 1.00; $I^2=0$%; nine trials); myocardial infarction narrowly failed to reach statistical significance.

There was no effect on all-cause mortality (number of trials not reported), cardiovascular mortality ($I^2=23.4$%; nine trials) and heart failure ($I^2=26.7$%; nine trials).

In studies on people with diabetes, more intensive targets reduced the risk of albuminuria progression (RR 0.90, 95% CI 0.84 to 0.96; $I^2=0$%; three trials). There was some reduction in progression of retinopathy (RR 0.81, 95% CI 0.66 to 1.00; $I^2=65.5$%; four trials) although this just failed to reach statistical significance; when one study with imbalances in baseline characteristics between groups was removed heterogeneity was reduced and result was statistically significant in favour of more intensive targets ($I^2=18.1$%).

Adverse events were reported inconsistently but where reported there were no statistically significant differences between the treatments for severe adverse events (five trials) and drug discontinuation (four trials). Information on other adverse effects were reported.

Subgroup analyses showed no evidence of different treatment effects for any particular subgroup. Meta-regression investigating possible effects of baseline characteristics showed no evidence of heterogeneity.

**Authors' conclusions**

Intensive blood pressure lowering regimens provided greater vascular protection than standard regimens but did not have any clear impact on risks of death and serious adverse events.

**CRD commentary**

The aims of this review were clearly stated in terms of the inclusion criteria for participants, study design and outcomes. Treatment targets were less clear as there was no clear delimitation between higher and lower targets. The search was not restricted by language or publication type and this will have reduced the risk of language and publication biases. The authors acknowledged that their tests for publication bias were likely to have been unreliable given the limited number of available studies. The review methods aimed to reduce possible reviewer error and bias. Quality was assessed.

Methods of data synthesis appeared generally appropriate. Statistical heterogeneity was assessed and investigated. There appeared to be evident clinical heterogeneity between studies with participants having both different diagnoses and differing baseline blood pressure levels. The targets for more or less intensive treatment varied to such an extent that
there was overlap in these categories between studies and in some studies the lower intensity targets appeared to be above those in current practice. No details were given about types of antihypertensive drugs used.

The authors noted that most of the included participants had additional risk factors that made it unclear whether results could be generalised to other groups (including those with hypertension alone). Because of this, and the wide variations in target levels, conclusions should be treated with some caution.

Implications of the review for practice and research
Practice: The authors stated that evidence supported guidelines that advocated more intensive blood pressure lowering regimes in high risk patient groups although results should be generalised with caution.

Research: The authors stated that further trials were needed to clearly define risks and benefits of blood pressure targets below those currently recommended, especially in defining which groups would benefit most.

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