**Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose: observations from traditional and Bayesian random-effects meta-analyses of randomized trials**

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**CRD summary**
This generally well-conducted review concluded that available evidence suggested intensive blood pressure control (135mmHg or lower) reduced the risk of macrovascular events (death or stroke) in participants with type 2 diabetes mellitus/impaired fasting glucose or glucose intolerance, but increased the risk of serious adverse events. The authors' conclusions are likely to be reliable.

**Authors' objectives**
To evaluate target blood pressure goals for participants with type 2 diabetes mellitus and those with impaired fasting glucose or glucose intolerance.

**Searching**
PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for papers published from 1965 up to October 2010, with no language limitations. Search terms were reported. Reference lists of review articles, meta-analyses and original studies were handsearched.

**Study selection**
Randomised controlled trials (RCTs) of antihypertensive therapy that enrolled at least 100 participants with type 2 diabetes mellitus or impaired fasting glucose/glucose intolerance were eligible for inclusion. Eligible trials had to enrol participants who achieved systolic blood pressure 140mmHg or lower in both arms and report on at least one year outcomes. Trials were also required to enrol participants who achieved systolic blood pressure in the intensive group of 135mmHg or lower, achieved systolic blood pressure in the standard blood pressure group of 140mmHg or lower, and had a systolic blood pressure difference between the intensive and standard blood pressure groups of at least 3mmHg. Trials where there was no significant difference in blood pressure between arms (below 3mmHg ) were excluded. Additional outcome measures included long-term macrovascular complications (such as all-cause mortality, cardiovascular mortality, myocardial infarction, stroke), microvascular complications (such as microalbuminuria, overt nephropathy, end-stage renal disease/dialysis), and serious adverse effects.

Data on included trial settings was not reported. The mean age of included patients ranged from 55 to 67 years. The proportion of men ranged from 34.5 to 82% (where reported). Glycated haemoglobin levels ranged from 7 to 11.5% (where reported). Final systolic and diastolic blood pressure varied (further details reported in the paper). Comparison groups were: intensive versus standard blood pressure lowering; benazepril/amiodipine versus benazepril/hydrochlorothiazide; candesartan versus placebo; doxazosine versus chlorothalidone; enalapril versus nifedipine; fosinopril/amiodipine versus amloidipine; perindopril versus placebo; perindopril-indapamide versus placebo; ramipril versus placebo; and valsartan versus placebo.

Two reviewers independently assessed studies for inclusion.

**Assessment of study quality**
Two reviewers independently assessed the quality of included trials by considering the adequacy of: allocation sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; completeness of reporting of outcome data; and handling of other sources of bias. Trials with high or unclear risk for bias for any one of the first three components were considered to be at a high risk of bias; otherwise they were considered to be at a low risk of bias. The authors did not state how any disagreements were resolved.

**Data extraction**
Two reviewers independently extracted data to calculate Peto odds ratios (ORs) and their 95% confidence intervals (CIs). Authors of primary studies were contacted for further information where necessary. The authors did not report...
how any disagreements were resolved.

**Methods of synthesis**

Pooled Peto odds ratios with 95% confidence intervals were calculated using random-effects meta-analysis. Heterogeneity was assessed using $I^2$. The association between systolic blood pressure and outcomes was assessed using meta-regression.

Subgroup analysis was conducted according to achieved systolic blood pressure in the intensive group: over 130mmHg but 135mmHg or lower (less intensive group) versus 130mmHg or higher (more intensive group). Sensitivity analyses were performed to assess effects of trial quality, blood pressure strategy versus others, and inclusion/exclusion of patients with impaired fasting glucose/glucose intolerance on the results.

Publication bias was assessed visually using funnel plots and by use of Begg and Egger tests.

**Results of the review**

Thirteen RCTs (37,736 participants) were included in the review. Sample sizes ranged from 102 to 11,140 participants. Nine trials were considered to be at low risk of bias; the rest were considered to be at an unclear or high risk of bias. Follow-up periods ranged from 23 to 78 months.

**Macrovascular outcomes**: The intensive blood pressure control group was associated with a 10% reduction in all-cause mortality compared with the standard blood pressure control (OR 0.90, 95% CI 0.83 to 0.98; $I^2=0\%$). There was no difference between the intensive and standard blood pressure control groups for the outcomes of cardiovascular mortality, myocardial infarction, heart failure, angina pectoris and revascularisation. The intensive blood pressure control group was associated with a 17% reduction in the odds of stroke compared with the standard blood pressure control group (OR 0.83, 95% CI 0.73 to 0.95; $I^2=27\%$).

**Serious adverse events**: The intensive blood pressure control group was associated with a 20% increase in severe adverse events compared with the standard blood pressure control group (OR 1.20, 95% CI 1.08 to 1.32; $I^2=78.8\%$).

**Microvascular outcomes**: Intensive blood pressure control was associated with significant reductions in microalbuminuria (OR 0.83, 95% CI 0.77 to 0.89; $I^2$ not reported) and overt nephropathy (OR 0.73, 95% CI 0.64 to 0.84, $I^2=61.3\%$) compared with the standard blood pressure control group. There was no difference between the intensive and standard blood pressure control groups for other measures of nephropathy (such as end-stage renal disease/dialysis or doubling of serum creatinine), retinopathy and neuropathy.

Results were similar in the sensitivity analyses.

No evidence of publication bias was found.

**Authors’ conclusions**

Available evidence suggested that intensive blood pressure control (135mmHg or lower) reduced the risk of macrovascular events (death or stroke) in participants with type 2 diabetes mellitus/impaired fasting glucose or glucose intolerance. There were no benefits for risk of other macrovascular or microvascular events. The risk of serious adverse events was increased.

**CRD commentary**

The review question was broadly stated. Three major databases were searched with no language restrictions, which minimised potential language bias. Minimal efforts were made to search the grey literature, so some relevant papers may have been missed. No evidence of publication bias was found. The review processes were conducted in duplicate, which minimised potential reviewer error and bias.

Trial quality was assessed using appropriate criteria and the results were reported. Methods used to combine trial results appeared appropriate. The overall sample size was large, although not all trials contributed to the analysis of adverse effects.

This was a well conducted review and the authors’ conclusions are likely to be reliable.
Implications of the review for practice and research

**Practice:** The authors stated that a treatment goal of 130 to 135mmHg was acceptable, and that more aggressive goals to 120mmHg could be considered in patients at higher risk of stroke. They also stated that at a systolic blood pressure lower than 130mmHg, there may be target organ heterogeneity, so reported cerebrovascular benefits should be balanced against an increased risk of severe adverse events and a lack of benefit for cardiac, renal and retinal outcomes.

**Research:** The authors did not state any implications for research.

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