Effects of intensive blood pressure reduction on myocardial infarction and stroke in diabetes: a meta-analysis in 73 913 patients

CRD summary
The review concluded that in patients with diabetes, protection from stroke increased with the magnitude of blood pressure reduction. No such relation was found for myocardial infarction. The authors’ conclusions reflect the evidence base and, although bias was likely in some studies, the conclusions are likely to be reliable.

Authors’ objectives
To assess the effects of blood pressure reduction on the risk of myocardial infarction and stroke in diabetic patients.

Searching
MEDLINE and The Cochrane Library were searched for eligible studies published up to April 2010; search terms were reported. There were no language restrictions. Reference lists of retrieved studies and review articles were searched. Doctoral dissertations, conference proceedings and pharmaceutical industry files were searched. Contact was made with experts in the field.

Study selection
Prospective controlled trials with a parallel group design that compared blood pressure lowering agents were eligible for inclusion in the review. Blood pressure lowering agents were angiotensin-converting enzyme (ACE)-inhibitors, angiotensin receptor antagonists (ARBs), calcium channel blockers (CCBs), diuretics and beta-blockers alone or in combination. Eligible studies compared agents against placebo or another active treatment.

Trials were required to include patients with diabetes mellitus at baseline (either a whole trial population or a subgroup reported separately), with stroke and/or myocardial infarction as prescribed endpoints and systolic blood pressure values both at baseline and at follow-up in all trial groups. Trial duration needed to be at least one year.

The included studies were comprised of either diabetic participants or subgroups of diabetic participants. Studies were published between 1996 and 2010.

The authors did not state how many reviewers selected studies for inclusion in the review.

Assessment of study quality
Studies were assessed for quality using Cochrane methods for assessing risk of bias: criteria included sequence generation of allocation, allocation concealment, masking of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias. Studies that scored a high risk of bias in any of the quality criteria were classified as lower quality studies.

The authors did not state how many reviewers assessed studies for quality.

Data extraction
Data were extracted on outcomes using an intention-to-treat approach. Relative risks (RRs) and 95% confidence intervals (CIs) were calculated.

Data extraction was performed independently by two reviewers. Inconsistencies were discussed and resolved by consensus.

Methods of synthesis
Studies were pooled in meta-analyses and summary relative risks and 95% CIs estimated using fixed-effect and random-effects models. In addition to the comparisons outlined in the inclusion criteria, some comparisons were made between a tight blood pressure lowering strategy and a less tight blood pressure lowering strategy. Heterogeneity was assessed using the X^2 test and the I^2 value. Publication bias was assessed by inspection of the funnel plot and a weighted
Subgroup analyses were performed according to trial quality score, trial population (only diabetics or diabetic subgroup), type of comparator (placebo, active treatment or blood pressure lowering), baseline systolic and diastolic blood pressure tertiles, final systolic and diastolic blood pressure tertiles and baseline-corrected differences in achieved systolic and diastolic blood pressure. Meta-regression analyses were performed. Clinical relevance of findings was defined as a relative risk reduction of 15% and 20%. Associated two-sided sequential monitoring boundaries were calculated and presented.

Results of the review
Thirty-one prospective randomised controlled trials (RCTs) with 40 arms of treatment (73,913 participants, range 134 to 13,101 participants) were included in the review. Six studies had low risk of bias, 10 studies had intermediate risk of bias and 15 studies had high risk of bias. Most trials were single-armed studies. Follow-up ranged from one to 8.4 years.

**Stroke:** Compared with control (active treatment, placebo or less tight blood pressure control), blood pressure lowering agents were associated with a significant reduction in the risk of stroke (RR 0.91, 95% CI 0.86 to 0.97, fixed-effect model, $I^2=33\%$; 29 studies). This reduction was consistent across subgroups, except for studies defined by type of comparator and by tertiles of the difference in achieved systolic blood pressure and diastolic blood pressure.

Compared with less tight blood pressure control, tighter blood pressure control significantly reduced the risk of stroke by 39% (RR 0.61, 95% CI 0.48 to 0.79, random-effects model, $I^2=0\%$; five studies).

In meta-regression analysis, risk of stroke significantly decreased by 13% (95% CI 5 to 20) for each 5mmHg reduction in systolic blood pressure and by 11.5% (95% CI 5 to 17) for each 2mmHg reduction in diastolic blood pressure.

**Myocardial infarction:** Compared with control (active treatment, placebo or less tight blood pressure control), blood pressure lowering agents were associated with a significant reduction in risk of myocardial infarction (RR 0.89, 95% CI 0.83 to 0.96, fixed-effect model, $I^2=38\%$; 24 studies) that was consistent across subgroups.

There was no evidence of a significant difference in risk of myocardial infarction when less tight blood pressure control was compared with tighter blood pressure control, although a trend favoured tighter blood pressure control. There was no evidence of a significant association between the extent of blood pressure reduction and risk of myocardial infarction.

For both outcomes, different types of blood pressure lowering agents, CCBs, ACE-inhibitors and ARBs were compared and results reported.

Linear regression tests of funnel plot asymmetry suggested no evidence of publication bias.

**Authors' conclusions**
In patients with diabetes, protection from stroke increased with the magnitude of blood pressure reduction. No such relation was detected for myocardial infarction.

**CRD commentary**
The review addressed a clear research question. Inclusion criteria appeared appropriate. A comprehensive search was conducted for relevant studies: a wide range of sources were searched, attempts were made to find unpublished studies and contact was made with experts in the field. Appropriate methods were used to extract data. The authors did not state how many reviewers selected studies and assessed included studies for quality, so reviewer error and bias could not be excluded. Studies were assessed for quality appropriately; half were at high risk of bias. Synthesis of studies, assessment of heterogeneity and assessment of publication bias were all appropriate; the authors acknowledged that publication bias was still a possibility. No heterogeneity was identified between higher and lower quality trials. Subgroup analyses and meta-regression were undertaken to further explore heterogeneity. Cumulative sequential analysis was performed to determine whether the evidence was reliable and conclusive.

The authors' conclusions reflect the evidence base and, although bias was likely in some studies, the conclusions are
likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that a policy of pursuing a more intense blood pressure lowering in patients with diabetes may be highly beneficial against stroke events, but to a lesser extent against coronary events. As coronary complications did not increase with intense blood pressure lowering, this strategy could be used for the prevention of any type of cardiovascular event.

**Research:** The authors stated that further studies were needed to test the efficacy of a tight control of blood pressure on the risk of stroke in patients with diabetes.

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