Comparative analysis of beta-blockers with other antihypertensive agents on cardiovascular outcomes in hypertensive patients with diabetes mellitus: a systematic review and meta-analysis

Balamuthusamy S, Molnar J, Adigopula S, Arora R

CRD summary
The authors concluded that beta-blockers increased cardiovascular mortality compared to renin-angiotensin blockade therapy in diabetic patients with hypertension but there was no increased risk of cardiovascular outcomes compared with control antihypertensive therapy. Differences between trials and lack of clarity about various aspects of the analyses mean that the authors’ conclusions may not be reliable.

Authors’ objectives
To compare the effects of beta-blockers with other antihypertensive agents on cardiovascular outcomes in hypertensive patients with diabetes mellitus.

Searching
MEDLINE, EMBASE, CINAHL and the Cochrane Library were searched for studies published in English between June 1996 and June 2007. Search terms were not reported. Published meta-analyses and reviews were also searched. Ongoing trials were sought from three specified websites. The authors stated that published and unpublished data were included in analyses, but that only published studies were eligible.

Study selection
Randomised controlled trials (RCTs) that compared the effects of beta-blocker therapy with other antihypertensive therapy on cardiovascular outcomes in hypertensive patients with diabetes mellitus were eligible for inclusion. Trials of primary diabetic cohorts with hypertension and trials of new onset diabetics were excluded. The primary review outcomes were myocardial infarction, stroke, cardiovascular mortality and total mortality. Secondary outcomes were fatal and nonfatal myocardial infarction and fatal and non-fatal stroke.

The included trials compared beta-blockers (atenolol or metoprolol) regimens with calcium channel blockers (amlodipine, diltiazem, felodipine, isradipine, renin angiotensin and verapamil) and renin-angiotensin blockade agents (captopril, enalapril, lisinopril, losartan and perindopril). In some trials, treatment arms classified as beta-blocker based used either beta-blockers or diuretics. All of the trials were in hypertensive patients with diabetes mellitus controlled with insulin, oral agents or a combination of both. Where reported, the mean age of patients ranged from 52 to 76 years. The duration of follow-up ranged from 2.7 to 8.4 years.

Two reviewers independently selected studies and resolved disagreements by discussion.

Assessment of study quality
Two reviewers independently assessed validity by considering treatment allocation, allocation concealment, blinding and use of intention-to-treat analysis.

Data extraction
The authors did not state how data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
Pooled relative risks (RR) and 95% confidence intervals (CI) were calculated using the fixed-effect and random-effects models. Heterogeneity was assessed using the $\chi^2$ and I$^2$ statistics. Beta-blockers were compared with all other antihypertensives, renin angiotensin blockade therapy and calcium channel blockers. Three trials in which patients were allocated to either beta-blockers or diuretics were analysed separately. It was not always clear whether trials classified as beta-blockers plus diuretic meant beta-blockers combined with diuretic, or beta-blockers, or diuretics. Funnel plots
were used to assess publication bias.

**Results of the review**

Eight RCTs were included (n=97,270). The authors stated that all the trials were 'open-label blinded'. All trials used intention-to-treat analysis.

There was no statistically significant difference for beta-blockers versus control, beta-blockers versus renin angiotensin blockade therapy, or beta-blockers versus calcium channel blockers for myocardial infarction, stroke or total mortality. Results for myocardial infarction were similar for trials in which patients were allocated to either beta-blockers or diuretics.

For cardiovascular mortality, there was no statistically significant difference for beta-blockers versus control, or for beta-blockers versus calcium channel blockers. Beta-blocker therapy was associated with a significant increase in the risk of cardiovascular mortality compared to renin angiotensin blockade therapy (RR 1.39, 95% CI 1.07 to 1.80); in two of the three trials included in this analysis, patients may have been allocated to either beta-blockers or diuretics.

**Authors’ conclusions**

Beta-blockers increased cardiovascular mortality compared to renin-angiotensin blockade therapy in diabetic patients with hypertension, but there was no increased risk of cardiovascular outcomes myocardial infarction, stroke, cardiovascular mortality and total mortality compared with control antihypertensive therapy.

**CRD commentary**

The review addressed a clear research question and inclusion criteria were clearly defined for study design, participants and outcomes. Inclusion criteria for intervention were ambiguous in that interventions that consisted of either beta-blockers or diuretics were included. Several relevant sources were searched and some attempts were made to minimise publication bias, but no attempts were made to minimise language bias. Methods were used to minimise reviewer errors and bias in the selection of studies and assessment of validity, but it was not clear whether similar steps were taken during data extraction. Only RCTs were included; their validity was assessed but not reported in full. Data were pooled using meta-analysis and heterogeneity was assessed. Significant heterogeneity was found for several of the analyses but potential reasons were not explored or discussed. In addition, there was a lack of clarity about reasons for the inclusion or exclusion of some trials from analyses, whether or not some analyses of beta-blocker regimes included patients allocated to diuretics, and why only a small proportion of the total number of patients were included in the various meta-analyses. Differences between trials and lack of clarity about various aspects of the analyses mean that the authors’ conclusions may not be reliable.

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

**Practice**: The authors recommended renin angiotensin blockade agents as first-line therapy in hypertensive patients with diabetes mellitus.

**Research**: The authors stated that adequately powered RCTs are required to compare calcium channel blockers and beta-blockers as add-on therapy to renin angiotensin blockade agents, with respect to metabolic and cardiovascular outcomes, in order to identify the most appropriate second-line antihypertensive agent in patients with diabetes and hypertension.

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