A meta-analysis of 94,492 patients with hypertension treated with beta blockers to determine the risk of new-onset diabetes mellitus

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CRD summary
This review concluded that patients receiving β-blockers, in particular those with a higher baseline body mass index and baseline fasting glucose level, have an increased risk of developing new-onset diabetes mellitus and stroke. Overall, the reliability of the findings is unclear given the numerous limitations of the review methods and data, therefore the conclusions should be interpreted with caution.

Authors' objectives
To determine the role of β-blockers in the risk of developing new-onset diabetes mellitus (DM) in patients with hypertension.

Searching
MEDLINE, EMBASE and PubMed were searched for articles published from 1966 to March 2007; the search terms were reported. Only English language articles published in peer-reviewed journals were included in the review.

Study selection
Randomised controlled trials (RCTs) that compared the use of β-blockers with other agents, in patients with hypertension, were eligible for inclusion. The included studies compared β-blockers with placebo, thiazide diuretics and/or nondiuretic antihypertensives such as angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers and calcium-channel blockers. The types of adults included varied between the studies, but most were mixed gender populations without myocardial infarction (MI) and/or coronary artery disease. The mean age was 50 to 76 years. The majority of studies assessed atenolol, propranolol or metoprolol. Eligible studies had to report the occurrence of new onset DM over at least a 1-year period. Other outcomes of interest included all-cause mortality, MI and stroke. Most of the included studies reported a follow-up duration of between 1 and 10 years, with most following up outcomes for between 3 and 5.8 years.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated for the outcomes. The primary outcome was only assessed in those patients without DM at baseline; definitions of DM varied between the studies.

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

Methods of synthesis
The studies were grouped by comparator, i.e. placebo, thiazide diuretics or nondiuretic antihypertensive agents. Pooled RRs with 95% CIs were calculated using either a fixed-effect model or, if there was evidence of significant heterogeneity, a DerSimonian and Laird random-effects model. Only the random-effects data are reported in this abstract. Heterogeneity was assessed using the \( \chi^2 \) test or \( I^2 \) statistic, or assessed visually using funnel plots. Potential sources of heterogeneity were investigated using predetermined covariates in a univariate regression analysis; significant covariates were further investigated using a multivariate regression analysis. Sensitivity analyses were performed after excluding trials of mixed intervention groups where patients could be randomly assigned β-blockers or diuretics. Analyses were performed for subgroups of younger (less than 60 years old) or older (at least 60 years old) participants.
Publication bias was assessed using the Egger weighted regression test.

**Results of the review**

Twelve randomised studies (n=94,492) were included in the review.

None of the analyses were associated with significant levels of statistical heterogeneity unless stated.

Compared with placebo, β-blockers were associated with an increase, but not a statistically significant increase, in new onset DM (2 studies). However, a significant increase in the risk of new onset DM was observed in one study of elderly patients (at least 60 years old; RR 2.13, 95% CI: 1.34, 3.38). A significant increase in new onset DM was also reported for β-blockers in comparison with non diuretic antihypertensives (RR 1.22, 95% CI: 1.12, 1.33; 7 studies); similar increases were reported for both elderly (RR 1.22, 95% CI: 1.10, 1.35; 5 studies) and younger (RR 1.17, 95% CI: 1.03, 1.33; 2 studies) patients. When compared with thiazide diuretics, β-blockers were associated with a non significant decrease in new onset DM (5 studies). When individual β-blockers were compared, atenolol was associated with the greatest risk of developing new onset DM in comparison with other agents (RR 1.35, 95% CI: 1.17, 1.56; 4 studies). One study reported that the risk with metoprolol was significantly higher in comparison with other agents (RR 1.34, 95% CI: 1.04, 1.73). A non significant reduction in risk of new onset DM was associated with propranolol (3 studies), but this result was heavily weighted by comparisons with diuretics.

Regression analyses showed that significant univariate predictors of new onset DM included a higher baseline fasting glucose level (odds ratio, OR=1.01, 95% CI: 1.00, 1.02), and greater systolic (OR 1.05, 95% CI: 1.05, 1.08) and diastolic (OR 1.06, 95% CI: 1.01, 1.10) blood-pressure. A higher baseline body mass index (OR 1.17, 95% CI: 1.01, 1.33) was a significant multivariate predictor. Secondary analyses showed that β-blockers were associated with a significant increase in the incidence of stroke (RR 1.15, 95% CI: 1.01, 1.30), but this finding was associated with a significant level of heterogeneity.

**Authors’ conclusions**

Patients receiving β-blockers, in particular those with a higher baseline body mass index and higher baseline fasting glucose level, have an increased risk of new-onset DM and stroke. There was also no observed benefit in mortality or MI for β-blockers in comparison with other agents.

**CRD commentary**

This review answered a clear review question, but might have missed relevant studies through the inclusion of only peer-reviewed studies published in English. The authors stated that they assessed publication bias, but did not report their findings. The lack of a validity assessment and the poor reporting of review methods make it difficult to determine the accuracy and reliability of the data. Attempts were made to investigate potential sources of heterogeneity and their effects, but there were various clinical differences between the studies, in particular with regard to the definitions of new-onset DM. In addition, the analyses were further hampered by the poor reporting of patient characteristics and study designs. The authors acknowledged these limitations and concluded that their analysis cannot be used to indicate a causal relationship between β-blockers and DM. The authors also drew conclusions about the risk of stroke, which was the focus of the review. Overall, it is difficult to assess the reliability of the findings given the numerous limitations of the review methods and data, therefore the conclusions should be interpreted with caution.

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

Practice: The authors stated that, given the limited evidence from this analysis and published studies showing the detrimental effects of new-onset DM, ‘the athergoenic potential of DM, whether primary or secondary (to medications), cannot and should not be ignored’.

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

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