Relation of beta-blocker-induced heart rate lowering and cardioprotection in hypertension
Bangalore S, Sawhney S, Messerli FH

CRD summary
This review found that in people with hypertension a reduction in heart rate achieved through use of beta-blockers increased the risk of cardiovascular events and death. There were some methodological problems with the review. It was possible that confounding factors may have influenced the results and this was not investigated. The conclusions may be unreliable.

Authors' objectives
To assess the role of heart rate reduction achieved through use of beta-blockers on the risk of cardiovascular events in people with hypertension.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for studies published between 1966 and May 2008; search terms were reported. Reference lists of identified studies, meta-analyses and relevant reviews were checked. The search was limited to English-language papers published in peer-reviewed journals. Studies published as abstracts only were excluded.

Study selection
Randomised controlled trials (RCTs) with at least one year follow-up that assessed beta-blockers compared to other agents or placebo as first-line therapy in people with hypertension were eligible for inclusion. The studies had to evaluate clinical cardiovascular outcomes and include data on heart rate. The outcomes of interest were all-cause mortality, cardiovascular mortality, myocardial infarction, stroke and heart failure. Mean changes in blood pressure and heart rate were reported.

Participants in the included studies had hypertension. Some studies excluded people with coronary artery disease, myocardial infarction, angina or cerebrovascular accident. Some studies included participants with coronary artery disease or left ventricular hypertrophy. Mean ages of participants ranged from 45 to 76 years. Four studies included only men and in others between 37% and 77% were men. Mean systolic blood pressure ranged from 145 to 195mmHg, diastolic blood pressure from 87 to 108mmHg and baseline heart rate from 68.8 to 80.1 beats per minute. Most participants (more than 78%) were treated with atenolol. Other beta-blockers used were oxprenolol, propranolol, metoprolol and pindolol. Comparators were placebo, amlodipine, lacidipine, bendrofluazide, hydrochlorothiazide, verapamil SR, losartan or a diuretic. Mean follow-up was 3.5 years.

Two authors independently assessed studies for inclusion. Disagreements were resolved by consensus.

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

Data extraction
Heart rates at end of treatment were extracted and change in heart rate between start and end of treatment were calculated. Relative risks (RR) with 95% confidence intervals (CI) were calculated for each outcome.

The authors stated neither how data were extracted for the review nor how many reviewers performed the data extraction.

Methods of synthesis
Where there was no heterogeneity (p>0.10) a fixed-effect model was used to pool data and otherwise a random-effects model was used. Pooled relative risks and 95% CIs were presented.
Meta-regression was used to investigate the relationship between heart rate at end of treatment with beta-blockers and risk of cardiovascular events. A weighted curve fit analysis was used to evaluate the best regression fit (p was considered significant at <0.05). Heterogeneity was assessed using the $X^2$ test and the $I^2$ statistic. Publication bias was investigated using Egger's test.

**Results of the review**

Nine RCTs (68,640 participants) were included: two placebo-controlled (7,984 participants) and seven active control (60,656 participants).

Tests showed no evidence of publication bias.

There was no significant difference in final blood pressure between beta-blocker and comparison group. There was a 12% lower heart rate in the beta-blocker group compared to the comparison group (p<0.0001).

There were no significant differences between beta-blockers and comparison in cardiovascular mortality (p=0.615; seven trials), non-fatal myocardial infarction (p=0.275; eight trials), heart failure (p=0.959; five trials), stroke (p=0.746, eight trials) and all-cause mortality (p=0.870, seven trials).

There was an inverse linear relationship between heart rate at end of treatment and risk of cardiovascular mortality (p=0.0001), non-fatal myocardial infarction (p=0.0001), heart failure (p=0.0001), stroke (p=0.0602) and all cause mortality (p=0.0000001), which indicated that relative risk increased as heart rate decreased.

**Authors’ conclusions**

Beta-blocker associated reduction in heart rate increased the risk of cardiovascular events and death in hypertensive people.

**CRD commentary**

The aims of this review were clearly defined in terms of inclusion criteria for study design, intervention and participants. A number of databases were searched. As studies other than published English-languages studies were excluded, it was possible that studies were missed. The method of data extraction was not described, so it was impossible to say whether steps were taken to reduce reviewer error or bias. The quality of the included studies did not appear to be assessed, so the reliability of data was unclear. The authors pooled outcomes from studies that compared different treatments (such as placebo-controlled trials and trials that used other hypertensive agents as the comparison), which may not have been appropriate. The authors conclusions regarding heart rate and cardiovascular events were based on comparisons between studies in which characteristics of participants and treatments appear to have varied. Therefore, it was possible that other confounding factors may have influenced the results. As the authors commented, most participants received atenolol as the beta-blocker and it may not be appropriate to generalise these results to other beta-blockers. Given these comments, the conclusions should be interpreted with caution and may be unreliable.

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

Practice: The authors did not state any implications for practice.

Research: The authors stated that further research was needed to establish the cause of the association between a decrease in heart rate (related to beta-blocker use) and risk of cardiovascular events.

**Funding**

The authors did not report how the study was funded, but one of the authors had received research funding/grants from GlaxoSmithKline, Pfizer, Novartis and CardioVascular Therapeutics.

**Bibliographic details**

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.