Beta-blockers for primary prevention of heart failure in patients with hypertension: insights from a meta-analysis

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CRD summary
The authors concluded that beta-blockers provided comparable benefits but no reduction in heart failure compared with other antihypertensive agents, but beta-blockers did increase stroke in elderly patients. Evidence appeared to support the authors’ conclusions, but the inadequate assessment of trial quality and limited search, make it difficult to determine the strength of the evidence.

Authors' objectives
To evaluate the efficacy of beta-blockers for the primary prevention of heart failure in patients with hypertension.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for studies published in journals between 1966 and May 2008. Search terms were reported. Reference lists of reviews, meta-analyses and identified studies were also screened. Studies published only as abstracts were excluded.

Study selection
Randomised controlled trials (RCTs) that compared the effects on heart failure of first-line beta-blocker monotherapy, compared with placebo or other hypertensive drugs, in adults with hypertension were eligible for inclusion. Patients could be of either gender, with or without other cardiovascular risk factors, with or without comorbidities, but had to be free of established heart failure. The minimum duration of follow-up had to be one year.

The primary review outcome was new-onset heart failure, as defined by the authors. Secondary outcomes included all-cause mortality, cardiovascular mortality, myocardial infarction (fatal and nonfatal) and stroke (fatal and nonfatal). The review also assessed the change in blood pressure over the duration of the study.

Just under half of the included trials evaluated the beta-blocker atenolol; other studies evaluated mixed beta-blockers (atenolol, metoprolol, pindolol) or oxprenolol. Most of the included trials compared beta-blockers with other antihypertensive agents including diuretics, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and calcium-channel blockers; other trials compared beta-blockers with placebo. The mean age of patients ranged from 52 to 76 years and just over half (56%) were male. The average weighted baseline systolic blood pressure was 172mmHg (range 149 to 197mmHg); the diastolic pressure was 96mmHg (range 86 to 108mmHg). Trials used different definitions of new-onset heart failure. The duration of follow-up ranged from 2.1 to nine years.

Three reviewers independently selected studies.

Assessment of study quality
The authors awarded one validity point for use of heart failure as a primary outcome and one point if the trial was ‘non-mixed’; zero points were awarded for mixed trials, in which patients could be randomised to either beta-blockers or diuretics in the beta-blocker arm.

Three reviewers independently assessed validity.

Data extraction
Two reviewers independently extracted point estimates of outcomes of interest from each trial.

Methods of synthesis
Pooled risk ratios (RR) and 95% confidence intervals (CI) were calculated using fixed-effect models in the absence of
significant heterogeneity (p>0.05); trials were weighted by the inverse of the variance. The DerSimonian and Laird random-effects model was used when significant heterogeneity was found. Heterogeneity was assessed using the Q and the I² statistics.

Subgroup analysis was used to examine the influence of the age of patients (elderly, with a mean age of 60 of more years, versus younger patients, with mean age of less than 60 years) and different beta-blockers. Univariate and multivariate regression analysis were used to examine the influence of baseline and end-point systolic and diastolic blood pressure, difference in blood pressure between treatments, age and duration of follow-up. The power of trials to detect a significant difference was calculated (details were reported). Sensitivity analysis was undertaken by excluding mixed beta-blocker/diuretic trials. Publication bias was assessed using funnel plot the weighted regression test of Egger.

**Results of the review**

Twelve RCTs were included (n=112,177 patients); five were mixed diuretic/beta-blocker trials.

Beta-blockers were more effective at reducing blood pressure than placebo; the weighted mean reduction was 12.6 mmHg for systolic blood pressure and 6.1 mmHg for diastolic blood pressure. Beta-blockers and other hypertensive agent had comparable effects on blood pressure.

There was no statistically significant difference in the risk of heart failure between beta-blockers and placebo (RR 0.77, 95% CI 0.60 to 1.01; three RCTs, n=8868 patients), or between beta-blockers and other antihypertensive agents (RR 1.00, 95% CI 0.92 to 1.08; nine RCTs, n=85,139 patients). The authors stated there was no heterogeneity.

There was no significant difference in the risk of heart failure for: beta-blockers versus diuretics (one RCT); beta-blockers versus angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (four RCTs); beta-blockers versus calcium-channel blockers (five RCTs); atenolol versus other hypertensive agents (five RCTs); beta-blockers in the elderly versus other antihypertensive agents (six RCTs); or beta-blockers in younger patients versus other antihypertensive agents (three RCTs).

For elderly and younger patients, there was no significant difference between beta-blockers and other antihypertensive agents in mortality, cardiovascular death or myocardial infarction. Beta-blockers were associated with a statistically significant increase in the risk of stroke in elderly patients (RR 1.19, 95% CI 1.11 to 1.28; six RCTs) and a significant reduction in the risk of stroke in younger patients (RR 0.78, 95% CI 0.65 to 0.94; three RCTs).

The authors stated that there was no evidence of publication bias for any of the analyses but data were not reported.

Results of meta-regression analysis were also reported.

**Authors’ conclusions**

Beta-blockers provided comparable benefits but no reduction in heart failure compared with other antihypertensive agents. Beta-blockers did increase the risk of stroke in elderly patients, so should not be used as first-line treatment for the prevention of heart failure.

**CRD commentary**

The review question was clearly stated and inclusion criteria were appropriately defined. Several relevant sources were searched but no attempts were made to minimise publication bias; publication bias was assessed and no evidence was reputedly found. It was not clear if any language restrictions had been applied. Appropriate methods were used to minimise reviewer error and bias during the review process. Only RCTs were included and the authors stated that they assessed validity, but criteria appeared inadequate; this made it difficult to judge the reliability of the results. Appropriate methods were used for the meta-analyses, heterogeneity was assessed, and various subgroup and sensitivity analyses were conducted. The authors acknowledged that for secondary outcomes, including stroke, trials in this review did not represent all data and that the apparently beneficial effects of beta-blockers on stroke in younger patients should be regarded with caution. Evidence appeared to support the authors’ conclusions, but the inadequate assessment of trial quality and limited search, make it difficult to determine the strength of the evidence.
Implications of the review for practice and research

**Practice:** The authors stated that given the increased risk of stroke associated with beta-blockers in elderly patients, beta-blockers should not be used for the primary prevention of heart failure, unless there are other reasons for its administration (such as prior myocardial infarction).

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

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