Efficacy and tolerability of nebivolol compared with other antihypertensive drugs: a meta-analysis

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CRD summary
The authors concluded that nebivolol 5 mg may have benefits in hypertensive patients compared to existing antihypertensives and may have a role in the first-line treatment of hypertension. Evidence appeared to support the authors' conclusions, but the limited search and inadequate validity assessment made it difficult to comment on the strength of the evidence underpinning the authors' conclusions.

Authors' objectives
To evaluate the efficacy and tolerability of nebivolol (a highly selective beta1-blocker) in patients with hypertension.

Searching
MEDLINE was searched to 2007 for studies published in full in English. Search terms were reported. In addition, reference lists of identified studies and reviews were screened.

Study selection
Randomised controlled trials (RCTs) that compared 5 mg/day nebivolol with placebo or active drugs (beta-blockers, calcium channel antagonists (CCA), angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor antagonists (ARA)) in patients with essential hypertension were eligible for inclusion. Studies had to include at least 25 patients per treatment arm, have a minimum duration of one month and report dosage regimen, antihypertensive effect, adverse events and statistical analysis. Studies evaluating combinations of drugs from the start were excluded. The review assessed the following outcomes: mean change in blood pressure (BP) from baseline; percentage of treatment responders at the end of treatment; percentage with normalised BP at the end of treatment; percentage with adverse events; and percentage withdrawing due to adverse events.

The included studies compared 5 mg/day nebivolol with the following: placebo; beta-blockers (atenolol 50 mg or 100 mg, metoprolol 100 bid or bisoprolol 5 mg); CCA (nifedipine SR 20 mg or amlodipine 5 mg to 10 mg); ACEI (enalapril 10 mg or lisinopril 20 mg); and ARA (losartan 50 mg). The duration of interventions ranged from four to eight weeks. Baseline systolic BP ranged from 151 mmHg to 169 mmHg; diastolic BP ranged from 98 mmHg to 107 mmHg. Most of the included studies defined normalised BP as diastolic BP 90 mmHg or less; other studies defined it as BP <140/90. Use of concomitant medications varied among studies.

Two reviewers independently selected studies. Studies on which they disagreed were excluded.

Assessment of study quality
The authors did not state that they assessed validity, but did comment on the level of blinding.

Data extraction
The authors stated neither how data were extracted for the review nor how many reviewers performed the data extraction. For each study, percentages of patients with outcomes of interest were extracted or calculated and odds ratios (OR) were calculated with 95% confidence intervals (CI).

Methods of synthesis
Pooled OR, relative risks (RR) and rate differences (RD) with 95% confidence intervals (CI) were calculated with p-values. The authors stated that a Mantel-Haenszel model with random effects of the data was used. Heterogeneity was assessed using the $X^2$ statistic.

Results of the review
Twelve RCTs were included (n= 2,653): 11 studies were double-blind; one was single-blind.
Antihypertensive response: response rates were statistically significantly higher in nebivolol compared to ACEI groups (OR 1.92, 95% CI: 1.30, 2.85, two studies, p=0.001) and all antihypertensive drugs combined (OR 1.41, 95% CI: 1.15, 1.73, nine studies, p=0.001). There was no statistically significant difference in response rates between nebivolol and beta-blockers (three studies), CCAs (three studies) and the ARA losartan (one study).

Normalisation of BP: normalised BP rates were statistically significantly higher in nebivolol compared to losartan groups (OR 1.98, 95% CI: 1.24, 3.15, one study, p=0.004) and compared to all antihypertensive drugs combined (OR 1.35, 95% CI: 1.07, 1.72, eight studies, p=0.012) and for nebivolol compared with CCAs (OR 1.44, 95% CI: 1.05, 1.96, three studies, p=0.024). There was no statistically significant difference between nebivolol and beta-blockers (four studies).

Adverse events: there was no statistically significant difference in adverse event rates between nebivolol and placebo groups (two studies) or between nebivolol and ACEI (two studies). Adverse event rates were statistically significantly lower in nebivolol groups compared to losartan groups (OR 0.52, 95% CI: 0.30, 0.89, one study, p=0.016), other beta-blockers (OR 0.56, 95% CI: 0.36, 0.85, four studies, p=0.007), nifedipine (OR 0.49, 95% CI: 0.33, 0.72, one study, p<0.001) and all antihypertensive drugs combined (OR 0.59, 95% CI: 0.48, 0.72, eight studies, p<0.001).

Withdrawal due to adverse events: rates of withdrawal due to adverse events were statistically significantly lower in nebivolol compared to CCA groups (OR 0.18, 95% CI: 0.08, 0.41, two studies, p<0.001) and compared to all antihypertensive drugs combined (OR 0.42, 95% CI: 0.19, 0.90, seven studies, p=0.025). There were no statistically significant differences between nebivolol and ACEI (two studies), ARAs (one study) and other beta-blockers (two studies).

**Authors' conclusions**
Results suggested that nebivolol 5 mg may have benefits in hypertensive patients compared to existing antihypertensives and may have a role in the first-line treatment of hypertension. The authors warned that the conclusions were not definitive.

**CRD commentary**
The review question and inclusion criteria were stated clearly. Limiting the search to English language reports identified in one database plus references may have resulted in the omission of other relevant studies and raised the potential for publication and language bias. Appropriate methods were used to minimise reviewer error and bias during the selection of studies, but it was not clear if similar methods were used for the extraction of data. Apart from blinding, study validity was not assessed and so results from these studies and any synthesis may not be reliable. Appropriate methods were used for the meta-analyses. Results of the reported assessment of heterogeneity were not reported, but overlapping 95% CIs in forest plots suggested homogeneity. A non-definitive conclusion appeared appropriate in view of the short duration of treatments evaluated. Evidence appeared to support the authors’ conclusions, but the limited search and inadequate validity assessment made it difficult to comment on the strength of the evidence underpinning the authors’ conclusions.

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.

**Funding**
None for the review. Two of the authors have spoken about or analysed data on nebivolol for Menarini.

**Bibliographic details**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adrenergic beta-Antagonists /adverse effects /therapeutic use; Antihypertensive Agents /adverse effects /therapeutic use; Benzopyrans /adverse effects /therapeutic use; Blood Pressure /drug effects; Calcium Channel Blockers /adverse effects /therapeutic use; Ethanolamines /adverse effects /therapeutic use; Humans; Hypertension /drug therapy; Losartan /adverse effects /therapeutic use; Randomized Controlled Trials as Topic

**AccessionNumber**
12008104592

**Date bibliographic record published**
01/12/2008

**Date abstract record published**
22/04/2009

**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.