Nebivolol in the management of essential hypertension: a review

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Authors' objectives
To evaluate the effectiveness of nebivolol, a beta-blocker, in patients with mild to moderate essential hypertension.

Searching
Medial literature published in any language since 1966 was identified using AdisBase (a proprietary database of Adis international, Auckland, New Zealand), MEDLINE and EMBASE. AdisBase search terms were 'nebivolol' and 'hypertension'. MEDLINE and EMBASE search terms were 'nebivolol' and 'hypertension'. Searches were last updated 12 May 1988. Additional references were identified form the reference lists of published articles. Bibliographic information, including contributory unpublished data, was also requested from the company developing the drug.

Study selection
Study designs of evaluations included in the review
Controlled trials. Except for non comparative trials, the design of studies included in the review was randomised, double-blind and, where necessary, double-dummy. The length of follow up of included studies ranged from 4 to 52 weeks.

Specific interventions included in the review
Nebivolol (0.5, 1.0, 2.5, 5.0 and 10mg) was compared with placebo, the beta-blockers atenolol (50 or 100mg) and metoprolol (100mg) and other classes of antihypertensive agents including calcium antagonists (nifedipine 20mg) and angiotensin converting enzyme (ACE) inhibitors (lisinopril 2.5-10mg, enalapril 10mg). The drug was also investigated in combination with hydrochlorothiazide (12.5 or 25mg) or enalapril (10mg)

Participants included in the review
Patients aged 18 to 78 years with essential hypertension with or without comorbid conditions. The mean age range was about 52 to 59 years. Where stated, patients had mild to moderate hypertension (defined as supine/sitting diastolic blood pressure (DBP) >/= 95 and </= 120 mm Hg after washout/placebo run-in period.

Outcomes assessed in the review
Outcomes were not defined a-priori. The primary efficacy end-point for included studies was the change from baseline in supine or sitting DBP. Other end-points included change from baseline in supine or sitting systolic blood pressure (SBP) and changes in standing DBP and SBP, which were generally assessed after 2 minutes in the upright position and after the sitting/supine measurement had been taken. Where stated, response to therapy was defined as a reduction in sitting/supine DBP to </= 90 mmHg or a fall from baseline values of 10% or of >/= 10 mmHg.

How were decisions on the relevance of primary studies made?
Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were included. No further information was presented on how decisions on the relevance of primary studies were conducted.

Assessment of study quality
The authors do not report the criteria used to assess validity, or how the validity assessment was performed.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.
Methods of synthesis
How were the studies combined?
Studies were combined in a narrative.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated. No statistical test for heterogeneity was conducted.

Results of the review
The review included two comparative trials, 13 randomised double blind controlled trials and 4 double dummy randomised controlled trials. Patient numbers per treatment group ranged from 14 to 211, with almost half of the studies including >100 patients.

Therapeutic efficacy:
Nebivolol 5mg once daily significantly reduces mean sitting or supine DBP. Significant reductions are maintained during continued therapy with no sign of rebound hypertension or tolerance. Nebivolol (5mg) produced similar reductions in resting DBP to atenolol 50 or 100mg once daily for up to 24 weeks and metoprolol 100mg twice daily for 12 weeks in hypertensive patients with or without comorbidities (concomitant type 2 diabetes mellitus or left ventricular hypertrophy). In addition, nebivolol (5mg) reduced sitting DBP in patients with hypotension to a similar extent to nifedipine 20mg twice daily after 12 weeks or lisinopril 40mg once daily after 8 weeks. Nebivolol (5mg) was more effective than enalapril 10mg once daily (usual dosage is 10 to 20mg once daily) after 4 or 12 weeks but not after 28 weeks of treatment. The drug had an additive effect when combined with hydrochlorothiazide 12.5mg once daily but not with enalapril. Nebivolol (5mg) significantly reduces sitting/ supine SBP compared with baseline or placebo. Standing SBP/ DBP was also significantly reduced compared with baseline or placebo and to a similar extent to reductions with atenolol, enalapril or nifedipine. Nebivolol 5mg/day and atenolol 100mg once daily, nifedipine 20mg twice daily or lisinopril < = 40mg once daily similarly and significantly reduced mean 24-hour ambulatory blood pressure. However, nebivolol (5mg) tended to prevent increases in early morning blood pressure better than nifedipine. In addition, nebivolol (5mg) reduces blood pressure loads by about 50% from baseline. Trough to peak rations of about 0.9 for supine or sitting DBP have been reported for nebivolol 5mg once daily, which is the same as that for nifedipine sustained release 20mg twice daily but higher than for enalapril 10mg once daily. Overall response rates (a decrease in sitting/ supine DBP to < / = 90mm Hg or a 10% or > / = 10mm Hg fall in DBP) to treatment with nebivolol 5mg once daily ranged from 58% after 4 weeks' therapy to 81% after 52 weeks' therapy. Response rates in nebivolol (5mg) recipients were significantly greater than in those receiving enalapril early (< / = 12 weeks), but not later (7 months), or metoprolol but did not differ between patients receiving nebivolol (5mg), atenolol or nifedipine. More nebivolol (5mg) than nifedipine recipients responded to treatment after 2 weeks.

Tolerability:
Adverse events were typically transient and mild to moderate; the type, severity and frequency were not dose-related. Adverse events experienced most often included headache, fatigue, paraesthesias and dizziness. In comparative trials the frequency and severity of adverse events reported in patients receiving once daily nebivolol 5mg or atenolol 50mg, enalapril 10mg or placebo were not significantly different. However, the overall incidence of adverse events was greater with nifedipine 20mg twice daily or metoprolol 100mg twice daily than with nebivolol. More atenolol or enalapril than nebivolol recipients reported impotence or decreased libido during therapy. In addition the incidence of fatigue increased from baseline in atenolol recipients but remained constant in nebivolol recipients during a 4-week treatment period.

Authors' conclusions
Current evidence indicates that nebivolol 5mg once daily is a well tolerated beta-blocker, which is as effective as once daily atenolol and other classes of antihypertensive agents. It may therefore be recommended as a useful alternative first-line treatment potion for the management of patients with mild to moderate uncomplicated essential hypertension.
**CRD commentary**

The review includes a clear objective, a good literature search and an attempt was made to identify unpublished studies. However, very little information is presented on the methodology used to conduct the review, for example, what were the specific inclusion/exclusion criteria used, how were decisions made on the inclusion of primary studies, how the validity of included studies was assessed and what criteria were used.

The authors’ conclusions seem to follow from the results but should be interpreted with caution in view of the above comments.

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

**Practice:** The authors recommend nebivolol as an alternative first-line treatment potion for the management of patients with mild to moderate uncomplicated essential hypertension.

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

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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.