



## EVIDENCED-BASED CARDIOLOGY

# Cochrane Corner: Antihypertensive efficacy of beta-1 selective beta blockers for primary hypertension<sup>☆</sup>



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### KEYWORDS

Hypertension;  
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**Abstract** Beta blockers are commonly used to treat hypertension. This Cochrane systematic review assessed the effect of beta-1 selective beta blockers on blood pressure (BP), pulse pressure (PP), heart rate (HR) and withdrawal due to adverse effects in patients with primary hypertension. Fifty-six randomized placebo-controlled trials were included, with a total of 7812 patients. These drugs reduced systolic/diastolic BP by 10/8 mmHg, PP by 2 mmHg and HR by 11 bpm; no difference was found between treatment and placebo regarding withdrawal due to adverse effects. Differences in efficacy were observed between the various beta-1 selective beta blockers, which may be due to methodological differences in the trials. The choice of an antihypertensive drug should take into account not only its efficacy in reducing BP but also its tolerability, its efficacy in preventing cardiovascular events, and other factors such as undesirable metabolic effects.

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### PALAVRAS-CHAVE

Hipertensão;  
Pressão arterial;  
Betabloqueadores

### *Cochrane Corner*: eficácia anti-hipertensora dos betabloqueadores seletivos beta-1 na hipertensão essencial

**Resumo** Os betabloqueadores são fármacos frequentemente utilizados no tratamento da hipertensão arterial. Esta revisão sistemática da *Cochrane* avaliou o efeito dos betabloqueadores seletivos beta-1 em doentes com hipertensão essencial, nomeadamente sobre a

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pressão arterial (PA), pressão de pulso (PP), frequência cardíaca (FC) e abandono devido à ocorrência de efeitos adversos. Foram incluídos 56 ensaios clínicos aleatorizados e controlados por placebo, correspondendo a 7812 doentes. A utilização destes fármacos levou a uma descida da PA sistólica/diastólica de 10/8 mmHg, da PP de 2 mmHg e da FC de 11 bpm; não se encontrou diferença significativa no que diz respeito a abandono devido a efeitos adversos entre estes fármacos e o placebo. Foram encontradas diferenças de eficácia entre os vários betabloqueadores seletivos beta-1, que poderão corresponder a diferenças na metodologia dos estudos. Na escolha de um fármaco para tratamento da hipertensão arterial deve ser tida em consideração a eficácia na redução da PA mas também a sua tolerabilidade, efeito na prevenção de eventos cardiovasculares e efeitos indesejados como os metabólicos.

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## Clinical question

What is the effect of beta-1 selective beta blockers on blood pressure (BP)?<sup>1</sup>

## Objectives

**Primary:** To quantify the dose-dependent effects of various doses and types of beta-1 selective beta blockers on systolic and diastolic BP in individuals with primary hypertension.

**Secondary:** To determine the effects of these drugs on pulse pressure (PP), heart rate (HR) and withdrawal due to adverse effects.

## Type and description of study

The authors performed a systematic review with meta-analysis of randomized, double-blind, placebo-controlled parallel or cross-over trials comparing any beta-1 selective beta blocker (atenolol, betaxolol, bevantolol, bisoprolol, esmolol, metoprolol, nebivolol, pafenolol and practolol) with placebo, with a duration of follow-up of at least three weeks and with BP measurements at baseline and at least once more between three and 12 weeks after starting treatment. Participants had to have baseline systolic BP of at least 140 mmHg or diastolic BP of at least 90 mmHg, or both, and plasma creatinine levels <1.5 times the normal level.

The following databases were searched: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Hypertension Group Specialised Register, and ClinicalTrials.gov up to October 15, 2015, as well as the references of published articles.

Two authors independently confirmed the inclusion of studies and extracted the data, and discrepancies were resolved by discussion or with the assistance of a third reviewer when necessary. The risk of bias was assessed.

The results are presented as mean differences in BP, PP and HR with 95% confidence intervals (CI) and as risk ratios (RR) for withdrawal due to adverse effects.

The meta-analysis was performed using a fixed-effects model unless significant between-study heterogeneity was present, in which case the random-effects model was used.

## Results

A total of 56 trials were identified (26 parallel and 30 cross-over) in 7812 primary hypertensive patients.

Overall, combining the effects of the recommended starting dose and twice the starting dose for each drug, beta-1 selective beta blockers reduced systolic BP by 10.4 mmHg, diastolic BP by 8.3 mmHg (95% CI 7.8-8.7), PP by 1.8 mmHg (95% CI 1.2-2.3) and HR by 10.9 bpm (95% CI 10.4-11.5), all with statistical significance. The RR of withdrawal due to adverse effect was 0.85 (95% CI 0.5-1.45), without statistical significance. The reduction in BP was greater at peak hours (12/9 mmHg) than at trough hours (8/7 mmHg). The quality of evidence as assessed with the GRADE Working Group grades of evidence<sup>2</sup> was low due to significant heterogeneity in the analysis and risk of bias exaggerating the effect.

Nebivolol decreased systolic/diastolic BP by 8/6 mmHg, estimated by pooling trials, since no significant differences were found between different dosages (5-20 mg/day). Atenolol, at doses of 50 mg (recommended starting dose) and 100 mg, led to reductions of 13/11 mmHg; comparisons between these two doses were inconclusive, although subgroup analysis showed a fall of 10/8 mmHg for a dose of 50 mg/day and of 15/13 mmHg for a dose of 100 mg/day. One trial was identified as an extreme outlier; if this outlier were removed, the overall decrease from doses of 50 mg/day and 100 mg/day was 11/9 mmHg. For metoprolol, pooled results of doses between 100 mg/day and 400 mg/day showed a decrease of 9/8 mmHg, without a significant dose-response effect; the recommended starting dose of 100 mg/day led to a reduction of 5/5 mmHg. The mean BP lowering effect of bisoprolol was 11/8 mmHg in pooled

results, without significant differences between doses from 5 to 20 mg/day. There were two extreme outliers, although the effect of removing these trials from the analysis was not reported.

Selection bias was difficult to assess because of poor reporting in the included studies. The risk of detection bias was considered to be high, but that of attrition bias was low, since there were few losses to follow-up. The risk of reporting bias was considered to be high since most studies did not report withdrawal due to adverse effects, as was the potential for publication bias, due to the existence of the asymmetry of funnel plots.

## Conclusions

Beta-1 selective blockers as monotherapy lowered systolic/diastolic BP by an average of 10/8 mmHg, PP by 2 mmHg and HR by 11 bpm. No difference was found between treatment and placebo regarding withdrawal due to adverse effects, and no graded dose-response effect was seen over the recommended dose range.

## Comment

This Cochrane systematic review analyzes a large number of trials with many participants to study the effect of beta-1 selective beta blockers, as a group and individually. This Cochrane Corner focuses on the drugs available on the market in Portugal. It presents the results on BP, PP and HR, and adverse effects by drug and by dose level. It is clear that increasing the dose does not necessarily increase the effect, in contrast to what would empirically be expected.

Despite the large number of trials included, the conclusions of the review point to low quality of evidence, mainly due to the significant heterogeneity in the trials and the presence of extreme outliers that could exaggerate the measured outcome effect. There were considerable methodological differences between trials, due to the long time intervals between the development and study of different drugs, as well as differences in time of BP measurement (peak or trough hours of plasma concentrations) and in study populations. Furthermore, BP was only measured in the physician's office, whereas ambulatory BP measurement is currently recommended.

## Clinical implications

Beta blockers were originally developed to treat angina but were also shown to be effective antihypertensive drugs. The mechanism by which they lower BP is not fully understood, and the fact that different beta blockers act on different receptors justifies a systematic review of beta-1 selective beta blockers separately from nonselective,<sup>3</sup> partial agonist<sup>4</sup> and dual alpha and beta blockers.<sup>5</sup> An overall assessment of the Cochrane systematic reviews on these different drugs suggests that beta-1 selective beta blockers are more efficacious than partial agonist and dual alpha and beta blockers and have similar efficacy to nonselective beta blockers, although differences in the methodologies of these reviews should be borne in mind. When comparing

subclasses, it is also important to consider tolerability and persistence,<sup>6</sup> effects on central BP and metabolic effects,<sup>7</sup> as these aspects appear to favor the nonselective beta blocker carvedilol and beta-1 selective beta blockers, particularly nebivolol.

The choice of an antihypertensive drug should take into account its efficacy in reducing BP, its other effects, and the patient's comorbidities. In the 2013 European guidelines for the management of hypertension beta blockers are one of the first-line drug classes recommended as monotherapy,<sup>8</sup> although with the caveat that these drugs have not been shown to reduce mortality and have less benefit in preventing target organ damage<sup>9</sup> and cardiovascular events.<sup>10</sup>

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

## Conflicts of interest

The authors have no conflicts of interest to declare.

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