Cochrane corner: beta-blockers for hypertension

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BACKGROUND

Beta-blockers refer to an assorted group of medications that block the action of endogenous catecholamines on beta-adrenergic receptors.[1] The β1 and β2 receptors are the primary beta-adrenergic receptors in the human cardiovascular system. Beta-blockers differ in their β1/β2-receptor selectivity and vasodilatory properties. Based on this diversity, beta-blockers have been categorised into first, second and third generation. First-generation beta-blockers, also referred to as non-selective blockers, possess equal affinity for β1 and β2 receptors. Second-generation (or selective) beta-blockers exercise more affinity for β1 than β2 receptors. Neither of these traditional beta-blockers has vasodilatory properties, which is an intrinsic characteristic of third-generation beta-blockers.[2]

Beta-blockers have been known to play a role in blood pressure control since 1949.[3] We summarise the findings of a Cochrane Review we published in 2017 on the comparative effects of beta-blockers as initial treatment for hypertension.[4] This is an update of a review we first published 10 years ago.[5–7]

Concise methods

We searched the Cochrane Library, MEDLINE, EMBASE and ClinicalTrials.gov using a comprehensive database-specific search string and checked reference lists of relevant publications, up to June 2016. We selected randomised trials with a duration of at least 12 months, which assessed the effects of beta-blockers as first-line therapy for hypertension, compared with placebo or other antihypertensive drugs. Eligible studies had to report one or more of the following outcomes: all-cause mortality, stroke, coronary heart disease, cardiovascular death and cardiovascular events (ie, coronary heart disease, strokes and heart failure). We used standard Cochrane methods to select eligible studies, assess risk of bias, extract and analyse data and assess the certainty of the evidence.[7]

MAIN RESULTS

Thirteen studies met our inclusion criteria. These studies compared beta-blockers with placebo or no treatment (four studies), diuretics (five studies), calcium-channel

Table 1 Summary of main results

Outcomes	Risk ratio (95% CI)	No of participants (no of studies)	Certainty of the evidence
Beta-blockers versus placebo			
All-cause mortality	0.99 (0.88 to 1.11)	23 613 (4 studies)	⊕⊕⊕⊖ Moderate*
Cardiovascular events	0.88 (0.79 to 0.97)	23 613 (4 studies)	⊕⊕⊖⊖ Low*†
Stroke	0.80 (0.66 to 0.96)	23 613 (4 studies)	⊕⊕⊖⊖ Low*†
Coronary heart disease	0.93 (0.81 to 1.07)	23 613 (4 studies)	⊕⊕⊕⊖ Moderate*
Adverse events	3.38 (0.82 to 13.95)	22 729 (3 studies)	⊕⊕⊖⊖ Low‡
Beta-blockers versus diuretics			
All-cause mortality	1.04 (0.91 to 1.19)	18 241 (5 studies)	⊕⊕⊕⊖ Moderate*
Cardiovascular events	1.13 (0.99 to 1.28)	18 135 (4 studies)	⊕⊕⊕⊖ Moderate*
Stroke	1.17 (0.65 to 2.09)	18 135 (4 studies)	⊕⊕⊖⊖ Low*‡
Coronary heart disease	1.12 (0.82 to 1.54)	18 135 (4 studies)	⊕⊕⊖⊖ Low*‡
Adverse events	1.69 (0.95 to 3.00)	11 566 (3 studies)	⊕⊕⊖⊖ Low*‡
Beta-blockers versus calcium-channel blockers			
All-cause mortality	1.07 (1.0 to 1.14)	44 825 (4 studies)	⊕⊕⊕⊖ Moderate†
Cardiovascular events	1.18 (1.08 to 1.29)	19 915 (2 studies)	⊕⊕⊕⊖ Moderate§
Stroke	1.24 (1.11 to 1.4)	44 167 (3 studies)	⊕⊕⊕⊖ Moderate§
Coronary heart disease	1.05 (0.96 to 1.15)	44 167 (3 studies)	⊕⊕⊕⊖ Moderate§
Adverse events	1.20 (0.71 to 2.04)	21 591 (2 studies)	⊕⊕⊖⊖ Low‡§
Beta-blockers versus renin–angiotensin system inhibitors			
All-cause mortality	1.10 (0.98 to 1.24)	10 828 (3 studies)	⊕⊕⊕⊖ Moderate§
Cardiovascular events	1.0 (0.72 to 1.38)	10 828 (3 studies)	⊕⊕⊖⊖ Low‡§
Stroke	1.30 (1.11 to 1.53)	9951 (2 studies)	⊕⊕⊕⊖ Moderate§
Coronary heart disease	0.90 (0.76 to 1.06)	9951 (2 studies)	⊕⊕⊖⊖ Low§¶
Adverse events	1.41 (1.29 to 1.54)	9951 (2 studies)	⊕⊕⊕⊖ Moderate§

*The two studies that contribute the most weight to this finding have high risk of bias.
†The risk ratio is too close to 1 and could easily include 1 if more trials are added.
‡Substantial heterogeneity of effect across studies.
§Only two to three studies have reported data on this outcome.
¶Imprecise results with a wide CI.

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blockers (four studies) and renin–angiotensin system inhibitors (three studies). Ten studies enrolled both men and women and the rest enrolled only men. Six studies enrolled participants aged 65 years or younger and the others enrolled participants aged 18 to 70 years (one study), 40 to 79 years (one study), 45 to 75 years (one study), more than 50 years (one study), 55 to 80 years (one study), 60 to 79 years (study) and 65 to 74 years (one study).

Most studies were conducted in Western Europe and North America. Among the nine studies that provided data on race, the proportion of participants categorised as white was 0% (one study), 44% to 48% (two studies) and 86% to 100% (six studies). We adjudicated most studies to have a high risk of bias because of weaknesses in study design, conduct and data analysis.

Table 1 shows the summary of beta-blocker effects on key outcomes. When used as initial treatment for hypertension, there is low-certainty evidence that beta-blockers may reduce the risk of cardiovascular events compared with placebo. This beneficial effect is a reflection of the substantial reduction in strokes with beta-blockers since there is little or no difference in coronary events between patients on beta-blockers and those on placebo. There is moderate-certainty evidence that this effect of beta-blockers on cardiovascular events is similar to that of diuretics and renin–angiotensin system inhibitors, but it is inferior to that of calcium-channel blockers. In addition, there is moderate-certainty evidence that calcium-channel blockers and renin–angiotensin system inhibitors prevent strokes more than beta-blockers. However, there is moderate-certainty evidence that beta-blockers have little or no effect on all-cause mortality when used as initial treatment for hypertension. This effect of beta-blockers on mortality is identical to that of diuretics and renin–angiotensin system inhibitors, but it is inferior to that of calcium-channel blockers. Finally, there is low-certainty evidence that hypertensive patients on beta-blockers are more likely to discontinue medications due to adverse events than patients on renin–angiotensin system inhibitors. Nonetheless, there is little or no difference in adverse events between beta-blockers and diuretics or calcium-channel blockers.

Overall, treatment of hypertension leads to reductions in cardiovascular events with the degree of reduction dependent on the type of medication used to initiate treatment. Starting therapy with calcium-channel blockers or renin–angiotensin system inhibitors produces higher declines in cardiovascular events than with beta-blockers.

LIMITATIONS

All included studies added other antihypertensive medications to the initial therapy. Thus, it is possible that the suboptimal effects seen with first-line beta-blockers could have resulted from the additional medications used. Atenolol (a second-generation or selective beta-blocker) was the beta-blocker used in three-quarters of participants in beta-blocker arms. Thus, it is not possible to say whether the suboptimal effectiveness and safety seen with beta-blockers is a property of atenolol or is a class effect of all beta-blockers. We did not find any trials that assessed the effects of vasodilatory beta-blockers in preventing mortality or cardiovascular events. The certainty of the evidence for most outcomes was low, implying that the likelihood of further research finding the effect of beta-blockers to be substantially different from the results of this review is high.

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