

## Should Beta-Blockers Still be Used as Initial Antihypertensive Agents in Uncomplicated Hypertension?

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### Abstract

Beta-blockers have long been used as first-line therapy for hypertension as their use had resulted in a reduction in cardiovascular morbidity and mortality in controlled clinical trials. A recent meta-analysis comparing beta-blockers to all other anti-hypertensive drugs taken together has found that stroke reduction was sub-optimal. Specifically, atenolol was associated with a 26% higher risk of stroke compared with other drugs. Several reasons may explain the less favourable outcomes with beta-blocker therapy. These include some adverse metabolic abnormalities such as dyslipidaemia and new-onset diabetes, and less effective reduction of central aortic compared with brachial blood pressure. Newer beta-blockers such as carvedilol or nebivolol are better tolerated. These beta-blockers have a vasodilating effect, which may beneficially affect systolic blood pressure in the aorta. Their long-term cardiovascular outcome in hypertension is still not known. Further studies would be required to show that stroke is adequately reduced by these newer beta-blockers. In conclusion, beta-blockers should not be the first drugs of choice in the management of uncomplicated hypertension. They may be used in addition to other anti-hypertensive agents to achieve blood pressure goals. However, in patients with angina pectoris, a previous myocardial infarction, heart failure and certain dysrhythmias, beta-blockers still play an important role.

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**Key words:** Central aortic pressure, Stroke

Beta-blockers have been widely prescribed to treat hypertension over the years.<sup>1</sup> While the benefits of these agents in reducing cardiovascular events in people with pre-existing heart disease are clear,<sup>2</sup> their clinical benefits in individuals with uncomplicated hypertension are less well-defined. Questions have been raised about beta-blockers as first-line treatment options in hypertension.<sup>3</sup> The precise mechanism(s) of beta-blockers in lowering blood pressure is uncertain, although a decreased sympathetic tone and renin production are thought to play a role.<sup>4</sup> The 2 Medical Research Council (MRC) trials completed in the 1970s<sup>5</sup> and 1980s<sup>6</sup> and 2 Swedish studies, the HAPPHY<sup>7</sup> and the MAPHY Studies,<sup>8</sup> are the earlier studies which provided supportive evidence for the use of beta-blockers for initial hypertension therapy. The 1993 JNC V guidelines suggested diuretics and beta-blockers as preferred initial agents as their use had resulted in a reduction in cardiovascular morbidity and mortality in controlled clinical trials.<sup>9</sup> However, in most of these trials, the improved cardio-vascular outcomes had been mainly achieved by combining a beta-blocker and a diuretic.<sup>3,10</sup>

Diuretics have been shown to be more superior to calcium channel blockers and angiotensin-converting enzyme inhibitors in treating high blood pressure and preventing cardiovascular events.<sup>11</sup>

In the MRC trial, it was evident that hypertensive patients receiving a beta-blocker had a stroke rate higher than the diuretic-treated patients and not different from patients treated with placebo.<sup>5</sup> The comparative efficacy between beta-blockers and diuretics in preventing cardiovascular events in hypertensive patients was recently assessed by meta-analyses comparing the low-dose diuretics with beta-blockers. These studies confirmed that low-dose diuretics had superior efficacy compared to beta-blockers in treating hypertension.<sup>12-15</sup> In a more recent meta-analysis of 13 randomised controlled trials that compared the use of beta-blockers with other antihypertensive drugs for the treatment of hypertension and 7 studies comparing the use of beta-blockers with placebo, beta-blockers were found to be less effective in cardiovascular outcomes compared to other antihypertensive agents.<sup>16</sup> When comparing with placebo or no treatment, beta-blockers were associated with a 19%

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reduction in stroke, which is half of that expected from previous hypertension trials.<sup>17</sup> The main results showed a 16% increase in the risk of stroke for beta-blockers compared with other antihypertensive drugs. Specifically, atenolol was associated with a 26% higher risk of stroke compared with other drugs. In addition, the relative risk of myocardial infarction and all-cause mortality was not significantly lowered by beta-blockers compared to placebo or no treatment. In a recent large meta-analysis of the effects of treatment on left ventricular mass in essential hypertension, beta-blockers seemed to have fewer beneficial effects on regression of left ventricular hypertrophy than other drugs.<sup>18</sup> One possible explanation is that beta-blockers result in reduced brachial blood pressure but less reduction in central systolic blood pressure compared to angiotensin-converting enzyme inhibitors, diuretics, and calcium antagonists.<sup>19-21</sup> Regression of left ventricular hypertrophy is also more closely correlated with central blood pressure than brachial blood pressure.<sup>22</sup>

Despite the relative inefficacy of beta-blockers, the incidence of adverse effects is substantial. In the MRC study, for every heart attack or stroke prevented, 3 patients withdrew from atenolol because of impotence, and another 7 withdrew because of fatigue.<sup>5,6</sup> The use of beta-blockers may be associated with reduced exercise capacity, reduction in peak expiratory flow rates, sleep disturbance with vivid dreams, lethargy, and cold hands and feet.<sup>3</sup> Some of the metabolic abnormalities associated with the use of older beta-blockers include a decrease in HDL-cholesterol, an increase in triglyceride level, a decrease in insulin sensitivity, increase in the incidence of new onset diabetes<sup>23</sup> and weight gain.<sup>24</sup> Thus, the risk/benefit ratio of beta-blockers is characterised by sub-optimal efficacy and multiple adverse effects. As we know, beta-blockers are a heterogeneous class of drugs. Although beta-blockers with vasodilating effects such as carvedilol, which has some alpha-blocker action, and the highly cardioselective agent nebivolol<sup>25</sup> are better tolerated and have fewer adverse effects, their long-term cardiovascular outcome in hypertension is not known.<sup>24,26</sup> Theoretically, the vasodilating effect of these beta-blockers may be able to lower central pressures than conventional beta-blockers by altering favourably the pattern of the pressure waves reflecting back from the periphery, thereby lowering the central pressure. This could be important in view of the outcome of the CAFÉ study, which showed that beta-blocker-based therapy had a sub-optimal effect on central systolic blood pressure.<sup>27</sup>

In conclusion, beta-blockers should not be the first drugs of choice in the management of uncomplicated hypertension. Beta-blockers, in particular, atenolol is associated with a higher rate of stroke and significant adverse effects. They may be used in addition to other antihypertensive agents to

achieve blood pressure goals. The use of beta-blockers still remains appropriate in patients with compelling indications such as angina pectoris, heart failure or post-myocardial infarction.

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