



# Should beta blockers remain first-line drugs for hypertension?

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## Summary

**Hypertension is an important risk factor for stroke and other cardiovascular events. National and international guidelines recognise five classes of drugs for the first-line treatment of hypertension, but the effectiveness of beta blockers has recently been questioned, especially in the elderly. However, achieving a lower blood pressure is more important than the choice of drug used in treatment. Many patients will need more than one drug to treat their hypertension. Beta blockers remain important and effective drugs, but age and comorbidities need to be considered when selecting a first-line drug.**

Key words: aged, atenolol, stroke.

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## Introduction

The antihypertensive drugs used in Australia are mainly diuretics, beta blockers, calcium channel blockers and antagonists of the renin angiotensin aldosterone system. The current National Heart Foundation guidelines for treating hypertension do not recommend a preferred first-line drug, but recognise beta blockers as an acceptable choice. However, recent publications have generated significant controversy about the role of beta blockers.

## Recent evidence about beta blockers

A meta-analysis has found that, compared to placebo, beta blockers are effective drugs and are associated with a 19% lower relative risk of stroke.<sup>1</sup> Compared to other antihypertensive drugs, there were no differences for all cause mortality or for myocardial infarction, but beta blockers did not reduce stroke to the same extent. This was reported as a 16% higher relative risk of stroke.

The majority of trials in the meta-analysis studied atenolol. When the analysis was restricted to other beta blockers, no significant differences were found in comparison with other antihypertensive drugs. However, this restricted analysis

contained only a few trials, with a low number of adverse events, so it was most likely underpowered to detect a difference. The authors of the meta-analysis concluded that all beta blockers are less effective than other antihypertensives and should not be used as first-line drugs in hypertension. However, the major differences observed between beta blockers and other antihypertensives are largely due to the influence of two trials.<sup>2,3</sup>

The recently published guidelines of the UK National Institute for Clinical Excellence (NICE)<sup>4</sup> no longer include beta blockers in their routine treatment algorithm for hypertension, citing concerns of lower effectiveness and a greater risk of diabetes especially in combination with thiazide diuretics. They also state that prospective trials with newer (more selective) beta blockers are needed.

## Other evidence

With the inclusion of more trials and re-analysis of the meta-analysis<sup>1</sup> according to age, it was shown that for patients with a mean age under 60 years, beta blockers were no different from other drugs in reducing the composite outcome (death, stroke or myocardial infarction). In those with a mean age over 60 years, beta blockers were associated with a higher incidence of stroke – relative risk of 1.18 (95% CI 1.07–1.30) – compared to other drugs.<sup>5</sup> An earlier review assessing diuretics and beta blockers also found that in patients over the age of 60, beta blockers failed to favourably affect clinical end points despite an effect on blood pressure.<sup>6</sup>

In these reviews the excess risk of beta blockers appeared to be largely due to trials enrolling patients with an average age over 60 years. No excess risk was seen in younger patients. This suggests that beta blockers should not be first-line in the elderly.<sup>5,6</sup>

## What matters most – lowering pressure or drug class?

Epidemiological studies consistently show that the majority of strokes are directly attributable to high blood pressure. An overview of reviews highlighted that the association of blood pressure and the risk of stroke is log linear.<sup>7</sup> This means that for any given absolute decrease in blood pressure from a baseline level, there is a similar relative risk reduction of stroke. The

difference in blood pressure reductions achieved by different drugs was often less than 1 mmHg, implying minimal difference between the drug classes.<sup>7</sup>

A collaborative trial of blood pressure-lowering treatment observed a greater risk reduction for stroke with regimens based on calcium channel blockers compared with those based on diuretics or beta blockers, but the results were of borderline statistical significance. The mean age of these patients was 65 years and there was no overall significant difference in major cardiovascular events between the drugs.<sup>8</sup>

Another analysis based on 61 prospective trials (12.7 million person-years at risk) concluded that throughout middle and old age, a person's usual blood pressure is strongly and directly related to vascular and overall mortality, without any evidence of a threshold down to at least 115/75 mmHg.<sup>9</sup> Stroke is much more common in older age than in middle age and, given the continuous relationship observed between blood pressure and the risk of death from vascular disease, the absolute benefits of a lower blood pressure are likely to be greatest for those at greatest absolute risk of vascular disease.

These large reviews suggest that reducing blood pressure is more important than the drug used. Achieving a lower blood pressure will result in a reduction in the risk of major adverse events.

### Antihypertensive effect of beta blockers

There are different types of beta blockers (Table 1). They vary in their lipophilicity, receptor specificity, mode of elimination, half-life, primary indications and cost.

The exact mechanism by which beta blockers exert their antihypertensive effect is uncertain. Possible actions include a

reduction of cardiac output (negative inotropic and negative chronotropic effect), an effect on vascular resistance, as well as an inhibitory effect on the release of renin (which is stimulated by the sympathetic nervous system) and central effects that may be influenced by the hydro- or lipophilicity of the beta blocker.

Many patients taking beta blockers in clinical trials required combination therapy, especially with thiazide diuretics, to achieve their target blood pressures. This has been raised as evidence that beta blockers have a weak antihypertensive effect. However, the need for combination therapy is not unique to beta blockers and many trials show better blood pressure control with combination therapy rather than single drug therapy, largely irrespective of the initial drug class used.

### Effect on arterial pressure

In clinical practice blood pressure is measured at the brachial artery. The brachial artery diastolic pressure is a good estimate of the central aortic diastolic pressure. However, the brachial artery systolic pressure does not accurately estimate central aortic systolic pressure as the peak systolic blood pressure is only one point on the systolic pulse wave.<sup>10,11</sup> The central aortic pressure may be more important than peripheral pressure to outcomes such as stroke, although this remains to be proven.

In patients older than 60 years the effect of drugs on peripheral artery blood pressure may not accurately predict the changes in central aortic pressure. Specifically with atenolol, the central aortic systolic pressure is not reduced as much as the peripheral systolic pressure. In practice this means that a reduction in brachial pressure is associated with a smaller reduction in central aortic pressure. In contrast, ACE inhibitors tend to cause a relatively small change in peripheral blood pressure but a proportionately higher fall in central aortic pressure.<sup>10</sup> A recent study comparing amlodipine and atenolol also found that atenolol had a significantly weaker effect on central aortic pressure.<sup>12</sup>

### Interpretation of the evidence

Although regarded as high level evidence, meta-analyses are only as useful as the trials they include. Meta-analyses that include heterogeneous trials, even when this is accounted for in the statistical modelling, need to be interpreted cautiously. In many ways they should be regarded as hypothesis generating rather than hypothesis proving. In the meta-analysis<sup>1</sup>, the authors listed limitations such as the inability to relate outcomes to the dose and dosing of the drugs. Their inability to adjust for blood pressure control also raises concern about the strength of the results.

The majority of trials of beta blockers in hypertension have used atenolol. The few 'non-atenolol' beta blocker trials mainly studied propranolol, a few studied metoprolol and fewer still studied other or newer more selective beta blockers. Furthermore, beta blocking drugs with vasodilating properties such as carvedilol<sup>13</sup> and nebivolol are different and may be

Table 1

#### Classes of beta blockers

Action	Adrenergic selectivity	Examples
Non-selective	beta <sub>1</sub> and beta <sub>2</sub>	propranolol sotalol*
Selective	beta <sub>1</sub> > beta <sub>2</sub>	atenolol metoprolol succinate metoprolol tartrate (sustained release) bisoprolol
Non-selective and vasodilating	beta <sub>1</sub> , beta <sub>2</sub> and alpha <sub>1</sub>	labetalol carvedilol
Non-selective and vasodilating (nitric oxide pathway)	beta <sub>1</sub> and beta <sub>2</sub>	nebivolol†

\* used primarily as a class III antiarrhythmic drug

† not currently available in Australia

more beneficial than traditional beta blockers. Whether the atenolol findings can be generalised to all beta blockers is therefore uncertain, however given the variety of drugs in the class it would seem premature to dismiss them all for the treatment of hypertension.

Beta blockers are effective at significantly reducing the risk of strokes compared to placebo or no drugs. Current data show that they are less effective at reducing stroke compared to other drugs. The evidence does raise questions about the efficacy of atenolol as a first-line drug in patients over the age of 60 years with primary hypertension and no other indications for a beta blocker. However, statements that beta blockers increase the risk of stroke are misleading.

Most patients, especially the elderly, will require several drugs to reach their blood pressure target. Beta blockers can be used in combination therapy and there may be particular indications for using them (see box). These can be secondary complications of hypertension or they may be conditions that coexist with primary hypertension. The type of beta blocker to use will be determined by the condition.

## Conclusion

It is unlikely there will ever be a single ideal first-line drug for hypertension and most patients will eventually need multiple drugs to control their blood pressure. Treatment needs to be individualised for all patients.

The choice of treatment should be influenced not only by underlying cardiovascular risk factors, comorbidities and potential adverse effects, but also by the age of the patient. Beta blockers remain a viable option in the treatment of hypertension and they should not necessarily be discontinued if the clinical condition is stable and controlled or if there is another indication for their use.

### Conditions where beta blockers are useful or indicated

- Ischaemic heart disease – angina (stable and unstable), postmyocardial infarction
- Tachyarrhythmias – supraventricular and ventricular tachycardia, atrial fibrillation, atrial flutter
- Chronic heart failure
- Palpitations
- Anxiety
- Essential tremor
- Migraine
- Glaucoma
- Thyrotoxicosis
- Portal hypertension

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