

# Beta blockers and their combinations in the management of hypertension

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Keywords: beta blockers, hypertension

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S Afr Fam Pract 2012;54(5):409-410

## Introduction

Beta blockers have been prescribed for the treatment of primary hypertension for a very long time. Currently, it is doubtful whether this is still a good idea. In fact, many are of the opinion that beta blockers should be relegated to a fourth-line drug, if used at all, for the treatment of hypertension. So what happened? Why the change of heart? Basically, two issues are driving this new view of beta blockers.

Firstly, beta blockers are cardioprotective when given to patients with a recent myocardial infarction and reduce subsequent mortality significantly. Certain types of beta blockers reduce mortality in patients with heart failure. This efficacy in secondary protection was translated to primary prevention without a critical assessment, and this is particularly the case in hypertension.

Secondly, reducing blood pressure by any means may not automatically translate into reduced cardiovascular morbidity and mortality. This happened with beta blockers in the primary treatment of hypertension.

## Previous trials with beta blockers

From 1985-2000, at least six trials have shown that, compared to placebo, various beta blockers were effective in reducing blood pressure. These beta blockers were propranolol, atenolol, metoprolol and pindolol.<sup>1</sup> Recent more critical analysis of these older trials has emphasised that beta blockers have often been evaluated and analysed when used together with diuretics. The assumption has been made that for the same degree of blood pressure reduction, the two classes of drugs are associated with the same effect on cardiovascular events. Doubts about the efficacy of beta blockers as monotherapy in hypertension were raised by Messerli et al in 1998.<sup>2</sup>

## More recent trials

In 2005, a meta-analysis by Lindholm et al evaluated 13 randomised clinical trials in which beta blockers were compared with other antihypertension drugs in the treatment of hypertension. It was found that the relative risk for stroke was 16% higher using beta blockers [95% confidence interval 4-30%] than it was for other drugs. There was no difference for myocardial infarction. When the effect of beta blockers was compared to placebo or no treatment, the relative risk reduction for stroke by using beta blockers was only about half the risk reduction for stroke using other antihypertension drugs. Compared to other drugs, beta-blocker treatment resulted in a 16% higher relative risk for a stroke. It was concluded that beta blockers should not be used as first-line monotherapy in the treatment of hypertension.<sup>3</sup>

The results of two recent large hypertension trials, namely the Losartan Intervention For Endpoint reduction in hypertension (LIFE) and the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), demonstrated the superiority of newer antihypertensive drugs over atenolol and the combination with diuretics.<sup>1</sup>

All of these data were obtained in mainly the elderly. The argument was raised: what about the use of beta blockers in younger patients? In a meta-analysis, Khan et al showed that beta blockers had no benefit of a reduction in mortality, myocardial infarction or stroke in younger patients.<sup>4</sup>

All of these and other data led to a change in the use of beta blockers for hypertension.

Reasons for the lack of cardiovascular protection provided by beta blockers are:

- *Reduced antihypertensive effect:* There is evidence that compared to other antihypertensive drugs, beta blockers may have suboptimal blood pressure-lowering ability.
- *Unfavourable haemodynamics:* The cardiac output is

low and the peripheral resistance high in the elderly who have hypertension. Beta blockers act by decreasing cardiac output. This may negatively affect the elderly. Therefore, beta blockers should not be prescribed to the elderly with isolated systolic hypertension. In a large evaluation of nearly 65 000 patients with uncomplicated hypertension, beta blockers that caused lower heart rates were associated with an increase in mortality, myocardial infarction and stroke.<sup>1</sup> Furthermore, beta blockers were not as effective in reducing central aortic blood pressure as other antihypertensive drugs.

- *Reduced compliance:* As a class, beta blockers are associated with many adverse effects and are not always well tolerated by many patients, especially the elderly.
- *Reduced effect on left ventricular hypertrophy:* In a large meta-analysis, beta blockers were shown to reduce left ventricular hypertrophy less so than other antihypertensive drugs.
- *Unfavourable metabolic effects:* The ability of beta blockers to negatively change lipids and the tendency to induce diabetes, especially when combined with thiazide diuretics, may have a particularly negative effect on young patients with hypertension.

### What about combinations?

Beta blockers that are combined with diuretics are classified not as preferred combinations, but as acceptable combinations.<sup>5</sup> These combinations have been shown to reduce cardiovascular events, but currently, the combination of renin-angiotensin blockers plus a calcium-channel blocker is preferred and seems to be superior to other combinations. Combined with diuretics, beta blockers are also subject to the same side-effects as the two components when used individually as monotherapy. This combination has an added blood pressure-lowering ability. Outcome data have shown that this combination reduces

events. However, the side-effect profile should be kept in mind.

Beta blockers can also be combined with a dihydropyridine type of calcium-channel blocker, e.g. amlodipine, but not with a nondihydropyridine type, e.g. verapamil. However, there is very little evidence of efficacy in this regard.

### What is the role of beta blockers?

Beta blockers should not be prescribed as monotherapy for hypertension. They can be added to other drugs for blood pressure control as a fourth-line drug. Beta-blockers should be prescribed earlier if there is a compelling indication, such as a myocardial infarction or cardiac failure. There is no outcome data yet on the newer type of beta blockers that have a vasodilator effect, such as carvedilol and nebivolol. They should not be used as a first-line drug. It remains to be tested whether or not these drugs will be able to reduce mortality and morbidity. Care should be taken when prescribing beta blockers to young people or the elderly if they have isolated systolic hypertension.

### Conclusion

Beta blockers should not be used as first-line monotherapy for the treatment of hypertension, but can be added at a later stage as a fourth-line drug to control pressure. There are still compelling indications for the use of beta blockers.

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