HIGH BLOOD PRESSURE

where are we at?

The recent literature has raised doubts about the role of ß-blockers for lowering blood pressure and the New Zealand Guidelines Group is updating the Assessment and Management of Cardiovascular Risk Guideline.

As we await the new guideline, general practitioners have asked us for some guidance for their day-to-day decisions on blood pressure management.

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Bottom Lines

What is the role of β-blockers in the treatment of hypertension?

- ß-blockers are appropriate first-line blood pressure lowering medicine when there is a concurrent medical condition for which ß-blockers have been proven effective, such as angina, previous myocardial infarction, heart failure or atrial fibrillation.
- In younger people ß-blockers are unlikely to have a significant benefit over other antihypertensive medicines. A thiazide is the preferred first-line medicine in all people.
- In older people a thiazide is the preferred first-line antihypertensive and ß-blockers are only used if there is a concurrent medical condition requiring a ß-blocker, or as adjunctive therapy to achieve good blood pressure control after an ACE inhibitor or calcium channel blocker.
- Start with the lowest dosage of ß-blocker for high blood pressure and increase every four weeks if required.

When a β-blocker is indicated, which one should we use?

- Metoprolol has proven benefits of improved morbidity and mortality from myocardial infarction and heart failure in people with hypertension.
- While ß-blockers in general, are looking less desirable as first-line blood pressure lowering medicines in uncomplicated hypertension, atenolol is potentially the least effective.

If β-blockers are not indicated, which antihypertensive is first choice?

- Thiazides are still the mainstay of blood pressure lowering therapy and should be used as first-line medicines unless there is a good reason not too. Adverse effects are generally not clinically significant, including the effects on blood glucose and serum cholesterol.
- At the time of deciding to treat high blood pressure, the use of aspirin and a statin should also be considered as a multi-faceted intervention to reduce the cardiovascular risk.

Choosing additional therapy: Calcium channel blocker or ACE inhibitor?

- The choice of medication to add to a thiazide depends on the other medical conditions of the person.
- When a ß-blocker is not indicated for concurrent conditions either an ACE inhibitor or calcium channel blocker is appropriate, especially in older people.
- It appears that a thiazide plus ACE inhibitor has a synergistic effect and is a suitable combination.

Medications for blood pressure management

Summary table

A combination of two or three classes is often required

Medication	Benefits	Risks	Suggestions
Thiazide	More effective than Ca channel blocker or ACE inhibitor in protecting against heart failure, as effective for other clinical endpoints.	More metabolic changes, but seldom clinically significant.	Usual first-line therapy in all age groups
ACE inhibitors	Synergistic with thiazides. As effective as Ca channel blockers. Reduces progression of renal failure. Effective in heart failure.	Acute renal failure when used with diuretic plus NSAID (Triple Whammy). Less effective in people of African or Caribbean descent.	Second-line therapy
Ca Channel blockers	As effective as ACE inhibitors. Benefits in angina	Drug interactions. May have unfavourable effects on heart failure. Risks with heart block.	Alternative second-line therapy
ß-blocker	Proven effectiveness in management of angina, post MI, heart failure, AF. Migraine prophylaxis.	Appear less effective at reducing cardiovascular risk in older people. Atenolol appears least effective. May aggravate peripheral vascular disease. Risks with asthma. Risks with heart block.	Hold in reserve unless another reason for using them

Rationales

What is the role of β-blockers in the treatment of hypertension?

Clinical effectiveness of ß-blockers

Along with thiazide diuretics, ß-blockers have traditionally been considered first-line therapy for high blood pressure. It appeared logical that, as ß-blockers had mortality benefits in secondary prevention, they would also be beneficial in primary hypertension. However, recent meta-analyses have raised some doubt about the role of ß-blockers for high blood pressure in the absence of concurrent medical conditions, such as symptomatic coronary artery disease, previous myocardial infarction, heart failure or atrial fibrillation.

In 1998 Messerli et al[2] published a systematic review of ten studies of hypertension in people 60 years or older. They found diuretics superior to ß-blockers for reducing all cerebrovascular events, fatal stroke, coronary heart disease, cardiovascular mortality and all cause mortality. In contrast, ß-blockers only reduced the odds of a cerebrovascular event.

More recently Lindholm et al[3] published a meta-analysis indicating that ß-blockers were superior to placebo in reducing stroke, but not myocardial infarction or mortality. Compared to other antihypertensive medicines, ß-blockers were not significantly better at reducing myocardial infarction or mortality, and were less effective in preventing stroke (number needed to treat with a non-ß-blocker antihypertensive to prevent one stroke = 209 (95% CI 112–834).[4] However, most of the studies involved atenolol, and when non-atenolol ß-blockers were analysed separately, compared to other antihypertensives there was no significant difference in stroke, myocardial infarction or mortality. The 'poor' outcomes appear to have been driven by atenolol.

Another meta-analysis by Bradley et al[5] compared ß-blockers with other blood pressure lowering medicines, and found that ß-blockers were no better than other blood pressure lowering medicines, and may be less effective for reducing stroke. However, similar to the Lindholm et al[3] meta-analysis, there was a predominance of atenolol studies (seven of the thirteen), and three propranolol studies, one oxprenolol study, one metoprolol study and one mixed ß-blocker study.

Khan and McAlister[6] repeated the meta-analysis of Lindholm et al[3] including three studies previously excluded. These investigators divided the studies into those people 60 years and older and those people younger than 60 years. Using a composite end point of myocardial infarction, stroke or mortality, the conclusion was that ß-blockers were significantly better than placebo in younger people for the composite endpoint, (though the study was underpowered to detect a difference in the individual endpoints) but not older people in whom only stroke was significantly reduced.

Compared to other antihypertensive medicines, there was no significant difference in the composite endpoint in younger people, but older people in the ß-blocker treatment group had a higher risk of events.

A theoretical basis for the lack of benefit of ß-blockers in older people is that in older people high blood pressure, particularly systolic blood pressure, is driven by low arterial compliance and increased vascular resistance. Hence vasodilatory medicines, such as thiazides, are likely to be more effective. In younger people high blood pressure is characterised by high cardiac output with normal or reduced peripheral resistance.

When a ß-blocker is indicated, which one should we use?

Adverse effects of ß-blockers

A 2002 meta-analysis[7] of 15 placebo-controlled trials involving more than 35,000 people, examined the adverse effects associated with ß-blockers. It determined that, annualised:

- There was no significant increase in depressive symptoms for people on ß-blockers, 6 per 1000 patients (95% CI; -7–19).
- 18 people in 1000 reported fatigue (95% CI; 5–30). Number needed to harm (NNH) = 57 per year of ß-blocker treatment. Higher association with the older ß-blockers.
- 5 per 1000 people reported sexual dysfunction (95% CI; 2–8). NNH = 199 per year of ß-blocker treatment.

The ß-blocker lipid solubility did not appear to be a factor in the rate of adverse effects. The selectivity of the ß-blocker may have a greater influence on some adverse effects than lipid solubility.

A later study investigating the adverse effects of ß-blockers in people with heart failure did not find a significant risk of fatigue associated with ß-blocker therapy, 3 per 1000 (95% CI; -2 to 9).[8]

In practice, however, people do appear to experience fatigue when ß-blockers are initiated and may complain of feeling very lethargic. The ß-blockers in heart failure study suggests that when starting a ß-blocker for hypertension or another cardiovascular condition, starting with a low dosage and increasing slowly (two to four weekly) should improve tolerance.

Atenolol has been one of the preferred ß-blockers in New Zealand for many years. Doubt was cast on the choice of atenolol for treating high blood pressure, when Carlberg et al[9] published part of their larger ß-blocker meta-analysis, focusing only on atenolol. There were nine atenolol studies identified – four comparing atenolol with placebo or no treatment and five comparing atenolol with an alternative blood pressure lowering medicine.

In the placebo studies the extent of blood pressure reduction was variable, but there was no significant improvement in all cause mortality, cardiovascular mortality or myocardial infarction, just a significant reduction in stroke. This has been a major debatable point because, paradoxically, it suggests that a reduction in blood pressure is not related to a reduction in cardiovascular events. This is clearly not in line with extensive evidence. Compared to other blood pressure lowering medicines atenolol, despite similar reductions in blood pressure lowering, was significantly less effective in reducing all cause mortality and appeared less effective in reducing cardiovascular mortality.

Coupled with the meta-analysis of all ß-blockers, showing a difference in outcomes between non-atenolol ß-blockers and atenolol,[3] this raised the question of whether atenolol was a poor choice of ß-blocker.

ß-blockers are a heterogeneous class of medicines. Soriano et al[10] investigated the effect of ß-blocker ancillary properties such as lipophilicity, intrinsic sympathomimetic activity (ISA) and selectivity and questioned the class effect of ß-blockers. ß-blockers that had the most positive effect post-myocardial infarction were lipophilic, $ß_1$ selective and without ISA. Metoprolol was more effective than atenolol.

If β-blockers are not indicated, which antihypertensive is first choice?

With the publication of the Antihypertensive and Lipid Lowering to prevent Heart Attack Trial (ALLHAT) study[11] the issue of which blood pressure lowering medicine to use appeared to be resolved, except a ß-blocker was not included in the study. The comparator medicines were a thiazide (chlorthalidone), an ACE inhibitor (lisinopril) and a calcium channel blocker (amlodipine). Doxazosin was originally in the comparator group but this arm was discontinued early due to a significantly higher rate of heart failure compared to chlorthalidone.

There was no significant difference between the three medicines for cardiovascular endpoints – stroke, angina, coronary revascularisation, peripheral arterial disease end stage renal disease or all cause mortality, or cancer and gastrointestinal bleeds. However there did appear to be less protection against heart failure for the calcium channel blocker and ACE inhibitor compared to the thiazide. The ACE inhibitor also appeared to be less protective for stroke than the thiazide (Table 1).

Table 1: ALLHAT Study. Risk of progressing to future medical condition[11]

	Thiazide	CCB	NNT	Thiazide	ACEI	NNT
Heart failure	7.7%	10.2%	40	7.7%	8.7%	100
Combined CVD				30.9%	33.3%	42
Stroke				5.6%	6.3%	142

NNT (number needed to treat) = Number of people treated with a thiazide instead of the comparator that would prevent one person having the event over six years.

Adverse effects

There were significantly more metabolic changes in the thiazide group but overall these did not translate into more cardiovascular events or all cause mortality. All groups had a reduction in total cholesterol at four years (0.49 mmol/L, 0.54 mmol/L and 0.53 mmol/L for the thiazide, calcium channel blocker and ACE inhibitor respectively).

The change in average serum potassium concentration at four years reduced by 0.1 mmol/L for the thiazide group, and increased by 0.1 mmol/L for the calcium channel blocker and ACE inhibitor groups. More people had a serum potassium concentration < 3.5 mmol/L in the thiazide group (8.9% compared to 1.9% in the calcium channel blocker group and 0.8% in the ACE inhibitor group).

The thiazide increased the average blood glucose 0.16 mmol/L compared to 0.03 mmol/L for the calcium channel blocker group (not significant) and a reduction of 0.08 mmol/L in the ACE inhibitor group (p=0.001).

The messages from the ALLHAT Study were:

- All people should be initiated on a thiazide as the first-line therapy for hypertension. For people requiring combination therapy, a thiazide should be included in the combination.
- Multiple blood pressure lowering medicines are usually required.
- ACE inhibitors do not offer a unique advantage in people with uncomplicated diabetes (no microalbuminuria).
- Significantly higher rate of heart failure in the calcium channel blocker group compared to thiazide group (10.2% vs. 7.7%; NNT = 40).
- Higher rate of combined cardiovascular disease in ACE inhibitor group compared with a thiazide (33.3% vs. 30.9%; NNT = 42).
- The potential adverse effects of the thiazide did not outweigh the benefits.

Unlike the ALLHAT study, the ASCOT-BPLA study in 2005[12] did include a ß-blocker. It used the composite end point of combined fatal coronary heart disease plus non-fatal myocardial infarction. It showed there was no significant difference between the ACE inhibitor (perindopril) added to the calcium channel blocker (amlodipine) compared to the thiazide (bendroflumethiazide) added to atenolol. However, all cause mortality was significantly less (NNT = 650 for one year) in the amlodipine plus perindopril group, as was the incidence of stroke and cardiovascular events and procedures.

Controversial aspects of the trial included:

- The use of a ß-blocker first, then a thiazide when a thiazide would normally be first-line, particularly as 63% of the study group was older than 60 years.
- The choice of atenolol as the ß-blocker raised doubts about whether the results could be extrapolated to all ß-blockers.
- The difference in blood pressure between the two groups (2.7 mmHg) could account for the difference in event rates.

The issue of the blood pressure difference was investigated in a paper published in the same journal.[13] Using multivariate analysis other factors accounted for approximately 50% and 40% of the difference between the groups for cardiovascular events and stroke respectively. HDL-cholesterol was the biggest contributor to cardiovascular events and blood pressure was the biggest contributor to stroke. The differences between the groups became no longer significant after adjustment for these differences.

Other factors to consider in the ASCOT-BPLA study were that only 19% of the people were on aspirin and 10% to 11% were on lipid lowering medicines. This compares to 36% on aspirin in the ALLHAT study. Additionally 17 to 18% of women were on HRT in the ALLHAT Study. This is contrary to the New Zealand guidelines where we expect people with a cardiovascular risk of more than 15% to be on aspirin and a statin as well as a blood pressure lowering medicine. Use of these adjunctive medicines may well reduce the importance of the choice of blood pressure lowering medicine.

	ALLHAT	ASCOT
Number	33,357 Mean 4.9 yrs follow up	19,257 Mean 5.5 yrs follow up
Population	Older than 54 years with hypertension plus at least one other CHD risk factor	40 - 79 years with hypertension plus at least three other CV risk factors
Medicines	Chlorthalidione, lisinopril, amlodipine	Amlodipine up to 10 mg, then add perindopril versus atenolol up to 100 mg, then add bendroflumethiazide
Endpoints	Combined fatal CHD or non-fatal MI	Combined fatal CHD or non-fatal MI
BP achieved	- Target 140/90 mmHg - Achieved goal for 68% thiazide, 66% calcium channel blocker, 61% ACE inhibitor - ACE inhibitor systolic blood pressure 2 mmHg greater than with thiazide	- Target 140/90 mmHg - Achieved goal for 53% of participants - Amlodipine arm achieve mean of 2.7 mmHg less than atenolol arm
Results	- NSD - primary endpoint - NSD - all cause mortality - Heart failure significantly increased with ACE inhibitor, calcium channel blocker - CVA and combined cardiovascular disease significantly increased with ACE inhibitor - Less increase in blood glucose in the ACE inhibitor group	- NSD – primary endpoint - All cause mortality reduced in amlodipine group (NNT ~ 650 for 1 year) - Total cardiovascular events and procedures, and CVA were significantly reduced in the amlodipine group - Risk of diabetes was significantly reduced in amlodipine group

NSD = No significant difference

Choosing additional therapy: Calcium channel blocker or ACE inhibitor?

The priority is to achieve the reduction of blood pressure. The choice of a calcium channel blocker or ACE inhibitor, after the thiazide, is less important than reducing the blood pressure itself. Choice of agent is likely to depend on tolerability and concurrent medical conditions such as angina and heart failure and possible drug interactions. Achieving good compliance with a blood pressure lowering medicine is likely to be more important than the choice between ACE inhibitor or calcium channel blocker.

Calcium channel blocker interactions

Care is required with calcium channel blockers, particularly diltiazem, because of drug interactions. Diltiazem inhibits the elimination of medicines metabolised by cytochrome P_{450} 3A4. This results in potentially significant increases in serum concentrations of some drugs e.g. simvastatin when diltiazem is added to therapy. Similarly diltiazem and other calcium channel blockers are susceptible to raised serum concentrations, when a macrolide antibiotic or azole antifungal is added to therapy, resulting in toxicity.

ACE inhibitor interactions

Care is required when an ACE inhibitor is used with a diuretic plus NSAID as renal function can deteriorate quickly. Of note 36% of the 33,357 people in ALLHAT had diabetes. Over the four years of the study there was no apparent additional benefit of ACE inhibitors over other blood pressure lowering medicines in people with uncomplicated diabetes (i.e. no microalbuminuria).

Drug-induced diabetes

Drug-induced diabetes differs to 'natural' diabetes associated with metabolic syndrome. We do not know the importance of an isolated increase in blood glucose concentration in the absence of metabolic syndrome. ACE inhibitors appear less likely to cause drug-induced diabetes. However, the clinical significance of drug-induced increased blood glucose is unclear, but the benefits of all blood pressure lowering medicines in cardiovascular outcomes appear to be greater in people with diabetes than without.

WHAT DO CURRENT GUIDELINES SAY?

Canadian guidelines, 2004

The Canadian guidelines suggest initial therapy from a choice of a thiazide, ß-blocker, ACE inhibitor, angiotensin II antagonist or long-acting dihyrdopyridine calcium channel blocker. However, a ß-blocker is not recommended as initial therapy in people older than 60 years with uncomplicated hypertension, or for isolated systolic hypertension.

New Zealand guidelines

The New Zealand Guidelines Group is updating the Assessment and Management of Cardiovascular Risk Guideline. The concept will still promote treating cardiovascular risk, rather than treating high blood pressure and other cardiovascular risk factors in isolation. This multifaceted approach to cardiovascular risk is likely to have a greater benefit than that seen in studies focusing only on blood pressure lowering.

We await the new guideline although it is likely that the choice of blood pressure lowering medicine will continue to be flexible, with an emphasis that:

- A thiazide is part of every blood pressure lowering regime – and first-line in uncomplicated high blood pressure including people with uncomplicated diabetes.
- ß-blockers are used when there is a concurrent medical condition that would benefit from them, but they are less suitable for addressing high blood pressure alone in older people.
- There is little difference between ACE inhibitors and calcium channel blockers as Step 2 blood pressure lowering medicines after a thiazide, although the use of an ACE inhibitor plus thiazide appears to have a synergistic advantage.
- It is hoped there will be an emphasis on methods to improve adherence to cardiovascular medicines.

UK – NICE guidelines, 2006

The NICE guidelines for hypertension changed in response to the ASCOT-BPLA. Basically the use of a ß-blocker in people with newly diagnosed hypertension was removed.

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