What's new in hypertension?

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How well are we doing in managing high blood pressure?

Hypertension is increasingly recognised as one of the most important determinants of cardiovascular pathology. We have traditionally recognised its role in the risk of stroke and coronary disease, aortic dissection and renal failure. We have occasionally seen congestive heart failure in young people with severe long-standing untreated (or undertreated) hypertension and consequent dramatic left ventricular hypertrophy. However, we have not perhaps fully appreciated that hypertension is the most common predisposing risk factor for the totality of heart failure, particularly the common occurrence of this among more elderly people with relatively preserved systolic left ventricular function.

It is also one of the most common determinants of chronic renal failure. Consequences are particularly prominent when hypertension is combined with other risk factors such as diabetes. There is much evidence to show that appropriate recognition, classification and ongoing treatment of hypertension is possible and could lead to far better outcomes than are presently the case. Surveys continue to show that, in most countries, more efficient treatment could improve long-term outcomes and the proportion of people with fully controlled hypertension remains small.

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New guidelines

The field of hypertension seems to be one where guidelines proliferate freely. It is interesting to observe some areas of convergence. A major thrust of the latest New Zealand guidelines, as in earlier versions, is to move hypertension out of the 'disease' concept; the vast majority of those with raised blood pressure cannot be viewed as suffering from a disease but having an elevated level of a particular risk factor. Prescribing an antihypertensive agent as a 'cure' for a patient presenting with a headache and a mildly raised blood pressure on this occasion only is the antithesis of good blood pressure management, tempting as it may be to seize on it as a solution. Surveys have shown that those with mild to moderate elevations of blood pressure (BP) have no more headaches or dizziness than those with normal BP.

The New Zealand Guidelines for the Management of Cardiovascular Risk[1] (summary available at http://www.nzgg.org.nz/guidelines/0035/CVD_Risk_Summary.pdf) integrate blood pressure into the equation for determination of overall absolute cardiovascular risk, with consideration of pharmacological management recommended when this exceeds 15% over the next five years. Of course there is concern for those with particularly high BP levels (as long as these are provably sustained on several occasions with minimisation of any factors likely to increase BP at the time of measurement) even if they are otherwise at low overall cardiovascular risk.

The Guidelines Committee debated these thresholds intensively but had to agree that there was no substantial proof of useful short to medium term (five years) benefit of treatment of patients with BP levels below 170/100 mmHg if risks are otherwise low. Above that level, concerns for the effects of the additional strain on heart and blood vessels override the strict risk consideration. The prototype risk calculation matrix developed in New Zealand some 12 years ago is now widely used here and variations of it are appearing regularly in overseas guidelines too. The corollary is that in those at high overall risk (especially the elderly) there is significant benefit from treating even mildly raised BP. The same rules, of course, apply to cholesterol levels.

Blood pressure measurement

There have lately been issues both over techniques of measurement and what measurements carry most significance. One survey in a prominent US medical institution showed that few nurses and no doctors fully followed the advised guidelines for BP measurement. There is an impression that standard manual sphygmomanometric expertise is actually deterio-

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rating and, with the phasing out of mercury sphygmomanometers because of environmental concerns, may become a lost art. Electronic sphygmomanometers, which are not always fully evaluated for accuracy and utilise a non-auscultatory method to derive blood pressure are increasingly being used and the recordings may be misleading. Recordings of BP rounded to '0s' (e.g. 140/80) raise the possibility of sloppy technique. In a recent FRACP examination, I watched as three of four otherwise good candidates underestimated a high systolic pressure by some 80mmHg by failing to use an adequate palpation technique in association with auscultation. Thankfully, the importance of using appropriately sized cuffs is increasingly appreciated. Blood pressure should be measured with the patient sitting with feet on the floor (studies have shown that crossing the legs raises BP!) but standing levels are also important to exclude an important postural drop.

Our traditional preoccupation with diastolic pressure has also been shown to be misplaced. As we prepare to mark the centenary of Korotkoff's demonstration of the use of auscultatory sounds to estimate features of the BP cycle,[2] perhaps we should recognise that we might have been better off without this technique! Correlation of both Phase IV (muffling) and Phase V (disappearance) of the sounds with true intra-arterial pressure is poor and, despite Phase V having been adopted as the preferred international standard for over 25 years, some practitioners continue to register Phase IV for preference (even some teachers, especially in nursing schools, appear to perpetuate this). Epidemiological studies have also shown that systolic pressure is by far the more important in predicting risk of future adverse events. One reason for the confusion is that, while systolic and diastolic pressures rise mainly in parallel up to the age of 50 years, after this, diastolic values tend to fall with the changing characteristics of the artery wall. A high systolic pressure in association with a low diastolic is actually a high-risk situation. The British and European risk charts now omit diastolic pressure.

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Is non-pharmacological management effective?

One of the more perplexing paradoxes of risk factor trends in Western populations is the rapid rise in body mass – a clear determinant of BP level in many studies – but decreasing levels of population BP (and decreasing age-standardised coronary death rate). Nevertheless, for the patient with raised BP we recommend decreasing excess body weight, decreasing moderate or high alcohol consumption, decreasing sodium intake and increasing aerobic exercise. These recommendations are all based on evidential benefit seen in (mainly short-term) clinical trials and are reasonable for all hypertensive patients. Their effect is, however, generally small in comparison with that of antihypertensive drugs and will not alone achieve goal BP levels for most patients. It certainly seems to be a most useful exercise where BP elevation is borderline and, for some, these efforts may obviate the need for drugs. Some practitioners advocate the use of 'natural' therapies but there is little if any objective evidence for long-term benefit of these. Stress reduction, sometimes aided by relaxation or meditation techniques, is recommended by others but again based largely on anecdote with little objective evidence to support it despite the attractiveness of the idea.

Just as important as such interventions to reduce BP levels non-pharmacologically, is the reduction of overall cardiovascular risk. Persuading a mildly hypertensive patient to stop smoking may be far more useful than treating the blood pressure. Reduction of animal fat may also reduce overall risk as well as having some effect on the BP.

Does the choice of drug affect outcome?

Choice of drug class

This debate has raged for many years, fuelled by the marketing needs of pharmaceutical companies with newer (and thereby more expensive) products. Arguments were made on the basis of surrogate endpoints but the need for properly controlled outcome trials was eventually recognised and many have reported in recent years. The biggest of these – the ALLHAT Trial[3] – reached a conclusion that no other drug group could outperform the humble (and cheap) diuretic.

The trial has been criticised as additional use of the comparator drug groups was deferred and led to unusual drug combinations. A substantial proportion of participants were African-American who may share some drug-responsiveness characteristics with Polynesians (less response to ACE inhibitors and beta blockers than Europeans). Some specific studies in defined groups have suggested some possible outcome differences: the ANBPS-2 study[4] in predominantly elderly European Australians showed a small benefit for those treated predominantly with an ACE-inhibitor over those given a diuretic and the LIFE study[5] in patients with ECG evidence of left ventricular hypertrophy showed the angiotensin-II receptor blocker, losartan, to produce slightly better outcomes than treatment with atenolol.

Most comparison trials have, like the ALLHAT trial, shown general equivalence of drug groups where BP lowering was equivalent. In ALLHAT, an alpha blocker arm was discontinued prematurely as BP reduction was inferior and outcomes, especially the incidence of heart failure, clearly less favourable than treatment with a diuretic. The latest comparison trial – 'VALUE'[6] (published June 2004) compared the dihydropyridine calcium

antagonist, amlodipine, with valsartan (an angiotensin-receptor blocker) and found a non-significant trend to fewer events with amlodipine associated with slightly better BP control in this arm. One reassurance obtained from comparative trials is that earlier concerns about the safety of calcium channel blockers (arising from cohort studies) appear to have been removed.

The conclusion would appear to be that BP-lowering by whatever means is the most important objective and any additional 'pleiotropic' effects of a specific drug or group are small by comparison and unproven.

Contests between drug classes may be less important than they seem when it is recognised that most patients with significant hypertension will require treatment with two or more drugs. It is fortunate that we have a number of reasonably well-tolerated drug classes to choose from and combine. The recent British guidelines have helpfully laid out some simple 'A,B,C,D' rules of combination (Figure 1), pointed out to me some years ago by Dr Howard Smith (personal communication). 'A' (ACE-inhibitors or angiotensin receptor blockers) or 'B' (beta-blockers) are best combined with either 'C' (calcium channel blockers) or 'D' (diuretics), rather than with each other, for increased efficacy. If side effects are a problem despite antihypertensive efficacy, then sideways substitution (A for B, C for D, or the reverse of these) may be appropriate.

Choice of drug within a class

Whether results seen in clinical trials with a particular drug can or should be assumed to apply equally to other drugs in the same class remains highly contentious with scientific, pecuniary and moral arguments. These are well set out in three short papers published last year and the issues are well known to New Zealand doctors in the therapeutic substitution policies implemented by PHARMAC. In the absence of head-to-head trials of specific agents within a class (which are rarely performed) we have to go along with the quote from Bertrand Russell mentioned in one of the papers *'The most savage controversies are about those matters to which there is no good evidence either way'.*

Figure 1

A (ACE inhibitor)	**B** (Beta blocker)
C (Calcium channel blocker)	**D** (Diuretic)

For efficacy, change or combine vertically (e.g. A with C or D)
If efficacy but side effects, move horizontally (e.g. A to B or C to D)

Some novel therapeutic approaches

The angiotensin II receptor blockers have been available (albeit in a restricted way) in New Zealand for a few years now. Their predominant use is as a substitute for ACE inhibitors when these are not tolerated. Some patients may get additional BP lowering effects by using these drugs in addition to maximum tolerated doses of ACE inhibitors but the effect appears to be variable and idiosyncratic.

Spironolactone has proven useful in severe heart failure but this is limited by side effects. Newer aldosterone inhibitors such as eplerenone may prove more tolerable and useful in both heart failure and hypertension.

Inhibiting the enzyme (neutral endopeptidase) that breaks down cardiac natriuretic peptides can produce powerful BP-lowering effects. Initial dual metalloproteinase inhibitors such as omapatrilat (which also inhibits angiotensin converting enzyme) have shown major antihypertensive potential but are associated with a worrying incidence of angio-oedema slowing their progress to availability.

An idea floated by Sydney physician, Gordon Stokes,[7] has been to add the use of nitrates where isolated systolic hypertension in the elderly has not been well controlled by more conventional therapy. Nitrates reduce the effect of reflected waves from the peripheral circulation which augment the systolic pressure peak centrally. Further evidence is awaited with interest.

References

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