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Management of hypertension

Addressing the impediments to effective management of hypertension will have major implications in the prevention of cardiovascular and renal adverse events.

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Although hypertension is the most common reason for GP consultations, there remains a large treatment gap, with fewer than 25% of patients with hypertension attaining target blood pressure. In addition, the prevalence of hypertension in Australia appears to be increasing. In 2001, the Australian Diabetes, Obesity and Lifestyle (AusDiab) study showed a prevalence of hypertension of 28.6% in adults in Australia, while some later, but significantly smaller, studies have suggested that the prevalence of hypertension may be much higher.[1,2]

Improved management of hypertension has major implications for the prevention of major cardiovascular and renal adverse events. Effective blood pressure management reduces the incidence of stroke, coronary heart disease (CHD), congestive heart failure (CHF) and peripheral arterial disease (PAD), and prevents the progression of renal disease to end stage when renal replacement therapy (dialysis and/or transplantation) is required.

This review summarises the impediments to the effective management of hypertension and discusses current Australian antihypertensive treatment recommendations. Further information can be obtained from the National Heart Foundation of Australia's publication *Guide to management of hypertension 2008* (updated 2009; available online from: http://www.heartfoundation.org.au/Professional_Information/Clinical_Practice/Hypertension/Pages/ default.aspx).[3]

Impediments to effective management of hypertension

Several factors act to impede the effective management of high blood pressure. These are summarised in Table 1 and discussed below.

Accuracy of blood pressure measurement

The issues affecting the accuracy of blood pressure measurement relate to machine accuracy, observer error and measurement technique.

Due to environmental concerns, there has been a movement away from the use of mercury sphygmomanometers without the simultaneous development of an equally robust and accurate replacement instrument. Electronic and aneroid sphygmomanometers need regular validation and, if inaccurate, require service and calibration. These

IN SUMMARY

- **The prevalence of hypertension appears to be increasing; however, the therapeutic gap remains unchanged, with most patients with hypertension not attaining target blood pressure.**
- **Therapeutic inertia appears to be one of the main contributors to the low rates of attainment of target blood pressure.**
- **Strategies such as mentoring programs that have been demonstrated to address therapeutic inertia need to be more widely implemented.**
- **Improved management of hypertension has major implications for the prevention of major cardiovascular and renal adverse events.**

instruments can be simply validated against a mercury sphygmomanometer using a 'Y' connector.

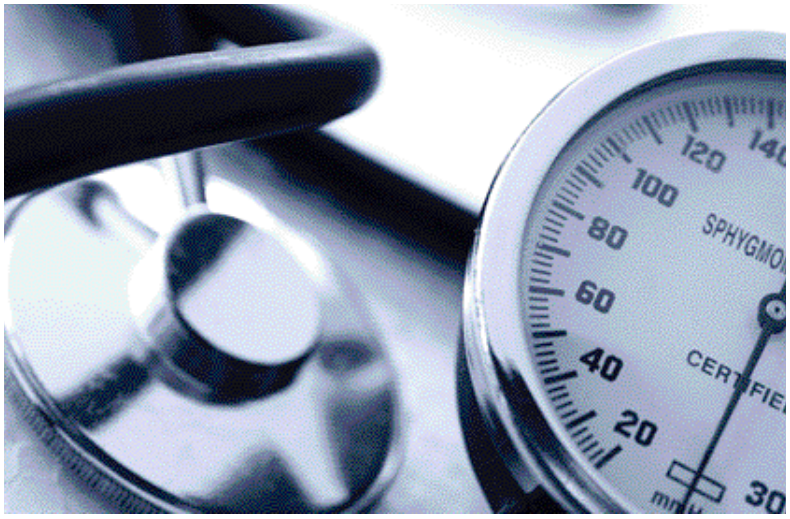
The well-known observer error of rounding to five or zero has been the subject of education and audit programs with some effect. Less well recognised is the tendency in a busy practice to question the patient while measuring blood pressure. The act of speaking raises blood pressure by 10 to 15 mmHg and may lead to inappropriately elevated readings. The use of incorrectly sized cuffs may also affect measurement accuracy: too small a cuff causes spurious elevations, whereas the use of an excessively large cuff may inappropriately decrease blood pressure readings.

The presence of a white coat effect or of a reverse white coat effect may also influence the accuracy of clinic blood pressure readings. To diagnose these and assess their magnitude, multiple blood pressure readings outside the clinic setting are needed. This may be achieved by home blood pressure monitoring by the patient using a validated home blood pressure monitor or by ambulatory blood pressure monitoring; however, different normal ranges apply (Table 2).

Unrecognised secondary hypertension

Patients who appear unresponsive to therapy may have an underlying secondary cause for their hypertension. Not all patients with phaeochromocytoma display the classical symptoms of tachycardia and episodes of pallor and sweating ('flushes'). Indeed, many may be totally asymptomatic as epitomised by the finding of phaeochromocytomas at postmortems performed for traumatic death.[4] In cases of genuine therapeutic resistance, 24-hour urinary catechol, metanephrine and normetanephrine levels (with a urinary creatinine level) should be measured to confirm phaeochromocytoma.

Similarly, the incidence of hyperaldosteronism (Conn's syndrome) is much higher than usually taught, being closer to 10% than 1% of patients with hypertension.[5] Further, more than 95% of patients with hyperaldosteronism are normokalaemic, negating the measurement of plasma potassium concentration as a screening test. If hyperaldosteronism is suspected or therapeutic resistance is being investigated, an aldosterone-to-renin ratio needs to be measured. However, this ratio may be affected by various antihypertensive



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agents, which may alter either the renin or the aldosterone levels. Beta blockers decrease renin levels, resulting in a spuriously elevated ratio. Other drugs that may affect renin and/or aldosterone levels, and thus the aldosterone-to-renin ratio, include angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), diuretics and the oral contraceptive pill.

Obstructive sleep apnoea is another frequently unrecognised cause of therapeutic resistance. Treatment of the sleep apnoea often restores therapeutic responsiveness in patients with hypertension. Thus it is appropriate to investigate sleep apnoea in patients who appear resistant to antihypertensive therapy if they snore and are overweight or obese.

Unrecognised use of prohypertensive substance

Agents such as NSAIDs, including COX-2 inhibitors, are in common use and cause therapeutic resistance in patients with hypertension. Recreational drugs such as amphetamines and cocaine, alternative medicines such as St John's wort and ginseng, and even foods such as liquorice may also be responsible for therapeutic resistance (for more complete lists see *Guide to management of hypertension 2008*, pp. 9,10).[3]

Additionally, the efficacy of ACE inhibitors and ARBs may be ameliorated or entirely abrogated by a high dietary salt intake. Measurement of the 24-hour urinary sodium excretion quickly elucidates whether this may be the cause. In assessing sources of unrecognised salt intake, one should be

Table 1. Impediments to effective management of hypertension

- Accuracy of blood pressure measurement
- Unrecognised secondary hypertension
- Unrecognised use of prohypertensive substances
- Failure to diagnose the need for pharmacological therapy
- Therapeutic inertia
- Compliance issues

Table 2. Upper limits of normal for home and ambulatory blood pressures*

	Systolic pressure (mmHg)	Diastolic pressure (mmHg)
Ambulatory		
24-h average	130	80
Awake average	135	85
Asleep average	120	70
Home measurement		
Daytime	135	85

* Adapted from the Heart Foundation's *Guide to management of hypertension 2008* (updated 2009).[3]

aware of cultural variations that may mask this on routine questioning. For example, various sauces used in Asian foods – soy, oyster, fish, teriyaki – are very high in salt, and kosher meat preparation is a significant contributor to salt intake.

Failure to recognise the need for pharmacological therapy

In patients with hypertension the presence of an associated condition such as diabetes or evidence of end-organ damage such as albuminuria (in the patient who doesn't have diabetes), left ventricular hypertrophy or vascular disease indicate the need for pharmacological therapy in addition to lifestyle measures. In the absence of these comorbidities, some patients with mild-to-moderate hypertension who are at high risk for cardiovascular events may not receive pharmacological therapy unless they are assessed appropriately. To differentiate those patients who require pharmacological therapy in addition to lifestyle measures, a cardiovascular risk assessment should be undertaken.

Therapeutic inertia

Therapeutic inertia is probably best defined as therapy not being increased despite patients having repeatedly elevated blood pressure readings. It is not unique to blood pressure management; it has also been reported in lipid management. Therapeutic inertia appears to be the main cause for the failure of patients to attain blood pressure targets as indicated by studies in both primary care (general practice) and specialist clinics.[6-9] Confronted with repeatedly elevated blood pressure readings, 80% of doctors do nothing, 3% change treatment to an equally inefficacious dose of another agent, and the remainder are equally split between increasing the dose of the existing agent or adding a second agent.

Compliance issues

Generally, compliance issues are of lesser importance in contributing to the failure to attain blood pressure targets than usually thought. Side effects of medication do affect compliance, with patients ceasing or reducing doses without informing their doctor, but the issue of once- or twice-daily dosing appears to have little impact. However, the issue of multiple medications is of importance. Many patients with hypertension, particularly those in older age groups, have several other conditions (e.g. diabetes and hyperlipidaemia) for which they also require medication, and often more than one drug for each condition. This requirement for multiple drugs may affect compliance in two ways:

- there may be confusion as to whether an individual dose of a particular medication has been taken, leading to its omission
- issues of cost may occur, with patients omitting to take one or more drugs until they can afford to purchase them again.

Improving blood pressure management

Blood pressure guidelines should in general provide a succinct, up-to-date (at the time of publication) summary of the evidence for who to treat and blood pressure targets and an integrated summary of the various clinical trials to provide therapeutic recommendations. Although guidelines are necessary to provide the framework for treatment, research has shown that of themselves they do little to improve practice and increase the number of patients attaining their appropriate blood pressure target.[10] Overlaying traditional education programs, such as lectures or seminars, do little to change practice.[10] Mentoring programs, whether undertaken by physicians, nurses or pharmacists, that provide stepwise guidance for increasing therapy do appear to improve outcomes.[11]

It has been suggested that the paucity of experience during both undergraduate

and postgraduate training in the ongoing management of chronic disease forms the basis of clinical inertia and for therapeutic gaps such as occur in hypertension management.[8] This inexperience results in a lack of confidence in how to increase therapy and to determine what are maximum acceptable doses and the preferred therapeutic combinations. Mentoring programs provide a milieu in which to acquire this experience and confidence and thus overcome therapeutic inertia.

Current Australian recommendations

The most recent *Guide to the management of hypertension 2008* (updated August 2009) provides new blood pressure targets and therapeutic recommendations.[3]

Blood pressure targets

As the risk for cardiovascular events as a function of blood pressure is a continuum, the general advice is to reduce blood pressure as far as is tolerated. For patients with end-organ damage or with conditions such as diabetes or previous cardiovascular events, a target of less than 130/80 mmHg has been set, and for patients with proteinuria greater than 1 g/day, a target of less than 125/75 mmHg has been set.

Therapeutic recommendations

Initiating therapy in uncomplicated hypertension

Regardless of the antihypertensive treatment chosen, all patients with hypertension should be advised on lifestyle modification, including the need for regular physical activity, smoking cessation, maintenance of an ideal weight, salt restriction and limiting alcohol intake. Recommendations for immediate initiation of antihypertensive treatment in patients are listed in Table 3.

As a consequence of accumulating evidence, thiazide diuretics are no longer recommended as first-line therapy for hypertension in patients under 65 years of age. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) demonstrated an excess incidence of new onset diabetes of approximately 2% per annum in patients treated with thiazides compared with those treated with ACE inhibitors.[12] This confirmed the incidence of new onset diabetes shown in the Medical Research Council (MRC) trials.[13,14] However, in patients aged over 65 years, in whom systolic hypertension becomes more prominent, thiazides have a demonstrated benefit.[15]

Beta blockers are no longer recommended as first-line therapy for uncomplicated hypertension in any age group. The Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm (ASCOT-BPLA) highlighted the propensity of combined thiazide and beta blocker therapy to cause new onset diabetes with an incidence approaching 5% per annum.[16] This trial sparked a number of meta-analyses focusing on the association between treatment with beta blockers and new onset diabetes, and all recommended that beta blockers no longer be used as first-line therapy in uncomplicated hypertension.[17]

ACE inhibitors and ARBs are now considered interchangeable. A large number of clinical trials have demonstrated equivalent outcomes for ACE inhibitor and ARB therapy. Unfortunately, all these trials have been powered to demonstrate noninferiority and, apart from the incidence of side effects in which ARBs have shown a definite advantage, the question of whether ARBs are the superior therapy has yet to be answered.

For patients with uncomplicated hypertension, an antihypertensive agent from one of the following classes is recommended for initial and maintenance therapy: ACE inhibitors, ARBs, dihydropyridine calcium channel blockers (CCBs) or low dose thiazide diuretics (for patients aged 65 years or over).

Combination therapy in uncomplicated hypertension

Combination therapy is necessary for patients with hypertension in whom blood pressure targets are not met on monotherapy. A preferred combination of an ACE inhibitor (or ARB) and a calcium channel blocker (CCB) has been recommended based on the findings of the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial.[18] Most trials of combination

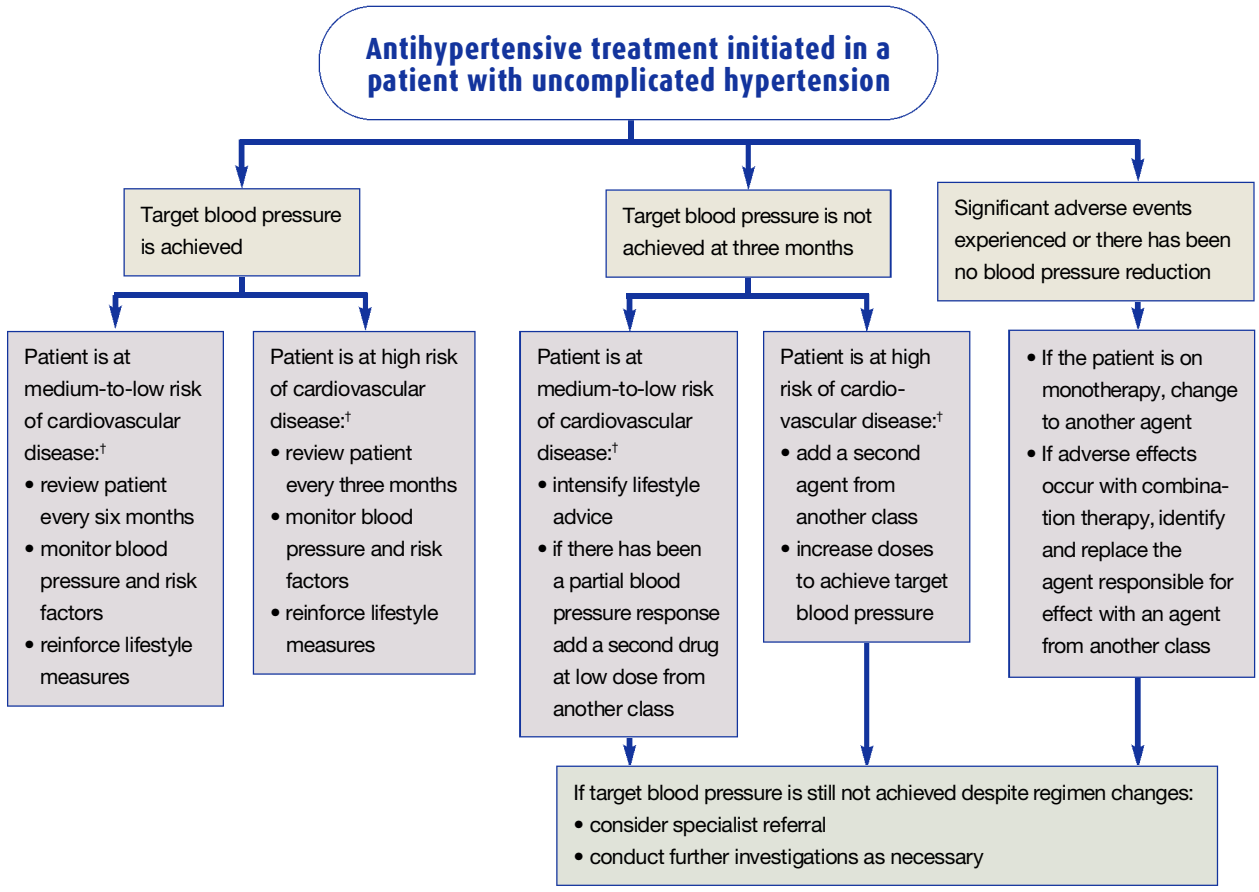
Table 3. Recommendations for immediate initiation of antihypertensive treatment*

- Patients with a systolic blood pressure of 180 mmHg or greater, and/or diastolic blood pressure of 110 mmHg or greater (i.e. grade 3 [severe] hypertension)
- Patients with isolated systolic hypertension plus a widened pulse pressure (i.e. a systolic blood pressure of 160 mmHg or greater and a diastolic blood pressure of 70 mmHg or less)
- Patients with evidence of end-organ damage or one or more associated conditions (such as diabetes, cerebrovascular disease, chronic kidney disease, peripheral arterial disease), irrespective of blood pressure
- Patients at high absolute risk of cardiovascular disease
- Early treatment should also be considered in Aboriginal and Torres Strait Islander adults with hypertension after careful assessment of cardiovascular risk, and in patients at a 10 to 15% risk of a cardiovascular event in the next five years as estimated using a risk calculator.

* Adapted from the Heart Foundation's *Guide to management of hypertension 2008* (updated 2009).[3]

continued

Maintenance and follow up of patients being treated for uncomplicated hypertension*



* Adapted from the Heart Foundation's *Guide to management of hypertension 2008* (updated 2009).[3]

† Cardiovascular risk assessed clinically and/or using a risk calculator.

therapy have compared ACE inhibitor or CCB based therapy with beta blocker based therapy; few have directly addressed the question of a preferred second agent in ACE inhibitor (or ARB) therapy. ACCOMPLISH compared treatment with amlodipine or hydrochlorothiazide added to treatment with the ACE inhibitor benazepril (not currently available in Australia). This trial was stopped early due to a 19.6% reduction in cardiovascular events (including cardiac death) in the CCB group compared with the thiazide group. For those with side effects from CCBs, the combination of a thiazide and ACE inhibitor (or ARB) still provides adequate blood pressure control.

The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) showed poorer outcomes with combined ACE inhibitor and ARB therapy than with either agent alone,[19] suggesting that the combination should be avoided. The findings of ONTARGET contrast with those of the Candesartan And Lisinopril Microalbuminuria (CALM II) study, in which no difference in adverse events between single and dual agent therapy was observed.[20] CALM II compared lisinopril 40 mg/day with candesartan 16 mg/day plus lisinopril 20 mg/day, whereas ONTARGET compared ramipril 10 mg/day, telmisartan 80 mg/day and the combination ramipril 10 mg/day plus telmisartan 80 mg/day. The different reported adverse outcomes may reflect the overall level of renin angiotensin system (RAS) blockade. In CALM II the levels of RAS blockade in single and dual agent therapy were equivalent. In contrast, in ONTARGET the level of RAS blockade in the dual therapy group was significantly greater than that in either of the single therapy groups. As a consequence adverse

events such as hyperkalaemia, which are dose related, would be predicted to be increased in the dual therapy group.

Thus, although combined therapy with an ACE inhibitor and an ARB may have benefit in selected groups (e.g. by reducing proteinuria while managing hypertension in patients with renal disease), its general use cannot be recommended until the adverse outcome question has been addressed with an appropriately designed and powered trial.

The flowchart on page 22 summarises the steps in the stabilisation, maintenance and follow up of patients after the initiation of antihypertensive treatment.

Conclusion

Hypertension remains the most common reason for GP consultations; however, despite guidelines and numerous education programs and audit programs, the significant therapeutic gap has remained unchanged. Recognition of the factors (such as therapeutic inertia) that are the main contributors to this and the widespread implementation of strategies (such as mentoring programs) that have been shown to work may in the longer term reduce this therapeutic gap. MT

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A list of references is available on request to the editorial office.

COMPETING INTERESTS: None.

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