Lowering blood pressure in 2003

John P Chalmers and Leonard F Arnolda

ABSTRACT

- The foundation of treatment for patients with hypertension is ongoing use of lifestyle measures such as physical exercise, weight reduction, and salt restriction.
- There should be emphasis on reduction of total cardiovascular risk, including smoking cessation and achievement of goal blood pressures.
- There are now five classes of first-line blood-pressure-lowering drugs — diuretics, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and calcium antagonists.
- In most patients, the choice of drug will be guided by the clinical situation in the individual patient, including the presence of target organ damage, diabetes, established vascular or kidney disease, or other comorbidities.
- In the absence of such clinical indications, start drug therapy with a low-dose diuretic.
- Combination therapy will be needed in around two-thirds of patients, and a diuretic will normally form one element of most combinations, with the second or third drug coming from among the remaining four.
- Consider the use of fixed-dose combinations to improve adherence to therapy.
- Use long-acting, once-daily preparations.

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THE RECOMMENDATIONS of the recent international guidelines on hypertension, the 1997 Sixth Report of the Joint National Committee (JNC VI)[1] and the 1999 World Health Organization–International Society of Hypertension Guidelines (WHO-ISH 1999),[2] had many principles in common. These included the need to assess and to consider overall cardiovascular risk rather than just blood pressure, to describe absolute risk rather than relative risk alone, and to stratify patients according to the severity of risk to determine prognosis and treatment.[1,2] However, these major guidelines differed in their recommendations for beginning drug treatment.

JNC VI recommended that, in the absence of compelling indications such as previous myocardial infarction or diabetic nephropathy, drug treatment should begin with diuretics or β-blockers. This was because, at that time, there was only limited evidence that the newer agents — such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs) or α-blockers — reduced morbidity or mortality in patients with hypertension.[1]

In contrast, the WHO-ISH 1999 guidelines recommended that any of these major classes of drugs could be used to initiate drug treatment, according to the clinical situation in the individual patient. This recommendation reflected the premise that the benefits of antihypertensive drugs were mainly dependent on their blood-pressure-lowering efficacy rather than on effects specific to particular drug classes.[2]

Most experts in the field agreed that these differences in recommendations arose from lack of evidence, and that randomised trials of the newer drugs were necessary to resolve the uncertainty.[1,2] Since the late 1990s, many clinical trials examining these issues have been completed, so that, by the turn of the century, there was sufficient evidence to establish that ACE inhibitors and CCBs do reduce the risks of coronary heart disease and stroke in patients with hypertension when compared with placebo.[3]

In the past year, the results of two of the most awaited trials have become available. These are:

- The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the largest comparative study of blood-pressure-lowering drugs ever completed,[4] and
- The Second Australian National Blood Pressure Study (ANBP2), a smaller head-to-head comparison of diuretics and ACE inhibitors, carried out entirely within general practice in Australia.[5]

Here, we review, primarily, the results of ALLHAT and ANBP2 in the context of the accumulated evidence about the newer classes of blood-pressure-lowering drugs reported since JNC VI and WHO-ISH 1999 were published.[1,2] Our review is made more timely by the release of JNC VII in May this year,[6] with recommendations based predominantly on the outcomes of ALLHAT[4] and the recent European Guidelines, released in June 2003 by the European Society for Hypertension jointly with the European Society of Cardiology.[7]

The importance of the effective treatment of hypertension has been reinforced in a most powerful way by the recent World Health Organization report (WHO Report 2002),[8] as highlighted in two shorter articles in the *Lancet*.[9,10] These reports confirm that, in developed countries, blood pressure is the single most important contributor to global mortality

Institute for International Health, University of Sydney, Sydney, NSW.

John P Chalmers, MD, FRACP, Professor of Medicine.

West Australian Institute for Medical Research, School of Medicine and Pharmacology, University of Western Australia, Perth, WA.

Leonard F Arnolda, PhD, FRACP, Professor of Cardiology.

Reprints will not be available from the authors. Correspondence: Professor John P Chalmers, Institute for International Health, University of Sydney, Newtown, NSW 2042. chalmers@iih.usyd.edu.au

from disease. A systolic blood pressure greater than 115 mmHg is estimated to be responsible for two thirds of all deaths from stroke and for half of deaths from ischaemic heart disease at the global level.[8-10] The reports estimate that intervention directed at lowering blood pressure and reducing cholesterol levels could halve the burden of cardiovascular disease.[8-10]

Trials outcomes before December 2002

The Blood Pressure Lowering Treatment Trialists' Collaboration, 2000

The major trials of newer antihypertensive agents reported before the end of 2000 were systematically reviewed by the Blood Pressure Trialists' Collaboration, which consists of the principal investigators of around 36 major randomised trials of blood-pressure-lowering treatment in patients with hypertension or related cardiovascular diseases.[3] It is coordinated by Stephen MacMahon and Bruce Neal from the Institute for International Health in Sydney. The second round of analyses, including the data from ALLHAT and ANBP2, has been submitted to the *Lancet* and should be published before the end of this year.[3] Meta-analysis of the data confirmed that ACE inhibitors and CCBs were safe and effective for preventing major cardiovascular events (a composite endpoint comprising myocardial infarction, stroke, heart failure and cardiovascular death) as well as stroke and cardiovascular death taken separately. In addition, ACE inhibitors were shown to prevent coronary heart disease and reduce total mortality.[3]

Comparisons were made between the "newer drugs" (ACE inhibitors, CCBs) and older drugs (diuretics and β-blockers lumped as "conventional therapy", without seeking to distinguish between them). The efficacy of ACE inhibitors was not different from diuretics/β-blockers for any outcome, whereas the analysis suggested that CCBs might be more effective than diuretics/β-blockers in preventing stroke, but marginally less effective in preventing coronary events or heart failure.[3] Direct comparisons between CCBs and ACE inhibitors suggested that the latter were more effective in preventing coronary disease or heart failure.

In summary: Overall, the net effect on cardiovascular morbidity and mortality of ACE inhibitors, CCBs and diuretics/β-blockers appears to be similar, although total numbers were small and confidence intervals were wide, so that clinically meaningful differences between treatments could not be excluded for some cause-specific effects on particular outcomes.

HOPE and PROGRESS trials

Both the HOPE[11] and PROGRESS[12] trials randomly allocated individuals to treatment arms on the basis of vascular disease rather than hypertension, to try to reduce morbidity and mortality in high-risk patients with a broad range of blood pressures.

In the PROGRESS trial, people with previous stroke or transient ischaemic attack were allocated to placebo or to active treatment with perindopril and discretionary use of the diuretic indapamide. Clear benefits of treatment included a 28% reduction in stroke (4% absolute reduction over four years) and a 26% reduction in major vascular events (a composite endpoint comprising stroke, myocardial infarction and cardiovascular death). Greater reductions, of the order of 40%, were observed with the larger blood pressure reductions obtained when patients routinely received the combination of perindopril and indapamide.

In the HOPE study, patients with established vascular disease (especially coronary heart disease), or with diabetes with or without vascular disease, were randomised to treatment with ramipril or placebo. Each component of the composite endpoint of stroke, myocardial infarction or cardiovascular death was reduced by treatment with ramipril. A modest difference in systolic blood pressure (3–4 mmHg) was observed throughout the trial.

In summary: These two studies confirm that, in patients with pre-existing coronary disease, cerebrovascular disease or diabetes, lowering blood pressure reduces the risk of cardiovascular morbidity and mortality in both patients with hypertension and those with normal blood pressure.[11,12]

Studies with angiotensin receptor blockers

The LIFE study provided the first evidence of the effects of ARBs on cardiovascular events in patients with hypertension and evidence of target organ damage, manifest as left-ventricular hypertrophy on electrocardiography.[13] This study compared initial therapy with the β-blocker, atenolol, and the ARB, losartan. The risk of the primary endpoint (death, myocardial infarction or stroke) was 2.8% in the atenolol group and 2.4% in the losartan group — 13% higher in patients treated with atenolol, mainly because of a significant 25% excess of strokes in this group, even though the reduction in blood pressure was similar in the two groups.[13]

While the authors of LIFE propose that the results establish that losartan confers specific benefits beyond lowering of blood pressure, it is equally possible that β-blockers (and atenolol in particular) are less effective in preventing strokes than thiazides. Indeed, the reductions in stroke in the Medical Research Council mild hypertension trial[14] and in stroke and heart attack in the Medical Research Council trial in older adults[15] were very much smaller (or absent) in the β-blocker arm of these studies than in the thiazide diuretic arm.[14,16]

The SCOPE trial was unable to demonstrate clear benefit of treatment with an ARB in elderly patients with hypertension, partly because of extensive use of antihypertensive therapy in the placebo group, 84% of whom received blood-pressure-lowering drugs.[17] The only other studies of ARBs in hypertension that report outcome data are three studies in patients with type 2 diabetes and hypertension.[18-20] These studies focused on how treatment affected the progression of renal disease. They provided evidence that ARBs slowed the progression of diabetic nephropathy, but were not designed to detect differences in cardiovascular outcomes, and were too small to confirm an effect on stroke, myocardial infarction or major cardiovascular events either individually or in aggregate.

In summary: ARBs are effective in lowering blood pressure and are well tolerated. They appear to be more effective than β-blockers in preventing adverse cardiovascular outcomes, especially stroke, in patients with hypertension, but evidence on the relative benefits of this group of drugs is still limited.

Review of the ALLHAT and ANBP2 trials

ALLHAT

ALLHAT was a randomised, double-blind trial designed to determine whether the incidence of the primary outcome, fatal coronary heart disease or non-fatal myocardial infarction, differed between treatments initiated with a diuretic (chlorthalidone) versus treatment initiated with a CCB (amlodipine), an ACE inhibitor (lisinopril) or an α-blocker (doxazosin).[4] Secondary outcomes included a composite endpoint (combined cardiovascular disease) as well as the separate elements of that endpoint (stroke, coronary heart disease, heart failure and cardiovascular death). More than 42 000 participants with hypertension, aged 55 years or older, were randomly allocated to the four treatment arms between 1994 and 1998. The doxazosin arm, involving some 9000 patients, was discontinued in January 2000 because of an excess of combined cardiovascular disease, heart failure and stroke.[21] The results of the remaining three arms of ALLHAT were reported at the end of 2002.[4]

The most striking feature of ALLHAT was the absence of any difference in the frequency of the primary outcome (fatal coronary heart disease or non-fatal myocardial infarction) or in all-cause mortality between any of the treatment groups, including the doxazosin group.[4,21] Another outstanding feature was the success of treatment with low-dose diuretic. Across a large number of comparisons of the diuretic versus the ACE inhibitor, the CCB and the α-blocker, the diuretic was either equally effective in the primary outcome, or superior in some secondary outcomes.[4,21]

The CCB, amlodipine, stood up very well in the comparison with the diuretic, with almost identical reductions in blood pressure, and almost indistinguishable effects in most outcomes. The exception was for prevention of heart failure, where the CCB was clearly inferior by around a third.[4] However, there was no suggestion whatever that the CCB increased mortality or morbidity due to cancer, severe bleeding, or coronary disease, as had been suggested by Furberg and colleagues, largely on the basis of observational studies.[15,22] This emphasises the importance of evidence from large, well conducted, randomised trials.

With the α-blocker, doxazosin, the reduction in systolic pressure was 2–3 mmHg less than that seen with the diuretic, and at the time that treatment arm was terminated, the risk of heart failure, combined cardiovascular disease and stroke were increased by 104%, 25% and 19%, respectively.[21] In the absence of any other major completed or ongoing trials with α-blockers, it seems reasonable to relegate this class of drugs to second line status, for use as adjunct therapy.

With the ACE inhibitor, lisinopril, the reduction in systolic blood pressure was also 2 mmHg less than that obtained with the diuretic, and the risks of combined cardiovascular disease, stroke and heart failure were increased by 10%, 15% and 19% respectively. However, there were some factors in the trial design that favoured the diuretic. The first was the larger fall in systolic blood pressure, which will have accounted for some of the greater benefits obtained with the diuretic. The second was the large proportion of African American patients (35%), as it is accepted that ACE inhibitors are less effective than diuretics in lowering blood pressure in African American people.[1,6] The third was the restriction in choice for additional blood-pressure-lowering drugs, so that the second choice, a β-blocker in most instances, was much less appropriate for combination with an ACE inhibitor than with a diuretic.[1,2,6,7] Finally, the criteria for heart failure were "soft", and when a "harder" heart failure endpoint was chosen (heart failure causing death or hospitalisation), the difference was no longer significant.[4]

In summary: ALLHAT establishes the prime importance of blood-pressure lowering for reducing the risk of cardiovascular morbidity and death in patients with hypertension, and shows there is little difference between the benefits conferred by diuretics, ACE inhibitors and CCBs, all of which are safe and effective. α-Blockers are less effective and should be kept as second-line drugs. CCBs are less effective for preventing heart failure, and not indicated for this purpose. Diuretics may have advantages in preventing stroke, though this advantage applies only in African American people.

ANBP2

ANBP2 was an open-labelled randomised study with blinded endpoints.[5] Over 6000 patients attending some 2000 general practices in Australia were randomly allocated to treatment, commencing with an ACE inhibitor (preferably but not exclusively enalapril) or a diuretic (preferably but not exclusively hydrochlorothiazide). After 4 years of follow-up, ANBP2 reported an 11% reduction in the primary endpoint (all-cause mortality and all cardiovascular events), which was only of borderline statistical significance ($P = 0.05$). The average age of patients in ANBP2 was 72 years and there were no African American patients in this trial. While there was a 17% reduction in this primary endpoint in men, there was no benefit in women.

The sample size of ANBP2 gave it limited power to detect small differences of the order of 10%–12% and to determine changes in subgroups and in secondary endpoints, such as cardiovascular death, and fatal or non-fatal stroke or myocardial infarction. The pre-specified primary endpoint (cardiovascular mortality and cardiovascular events)[23] was changed in the main study report.[5] However, some of the strengths of ANBP2 were that the reductions in blood pressure were much closer, and flexibility in choice of

additional blood-pressure-lowering drugs made the comparison between ACE inhibitor and diuretic fairer in many ways than that in ALLHAT.

Comparison of ANBP2 and ALLHAT

While the primary and secondary endpoints were different in the two studies, it is notable that the comparison for the primary outcome revealed no significant difference between ACE inhibitor and diuretic in ALLHAT, and only a marginally significant 11% difference in favour of the ACE inhibitor in ANBP2.

The biggest difference between the trials was in the populations being studied. In ALLHAT, participants were younger (mean age 67 years versus 72 years in ANBP2), and 35% were African Americans, whereas there were no African American participants in ANBP2. The importance of the African American cohort in ALLHAT is evident in the results for stroke. While the results for stroke risk may appear different — no significant difference in ANBP2 and 15% advantage to the diuretic in ALLHAT — there was no difference in stroke risk in the non-African American participants in ALLHAT. Thus, the appropriate conclusion for an Australian population, taking the two studies together, is that the benefits of both classes of drug in reducing the risk of stroke are much the same. Similarly, when the risk of a first coronary event (fatal or non-fatal) is examined, being the primary outcome for ALLHAT and a secondary outcome for ANBP2, it is evident that there is no significant difference between diuretics and ACE inhibitors in either study.

In summary: The main conclusions from these two studies are that differences between the benefits of different drug classes are very slight and restricted to cause-specific effects on particular outcomes, and that the key is effective reduction in blood pressure.

Interpretation of the evidence — old and new

When all the evidence is reviewed, including that leading up to JNC VI and WHO-ISH 1999,[1,2] more recent trials, and finally ALLHAT and ANBP2,[4,5] the messages that emerge are that:

- There are now five first-line groups of blood-pressure-lowering drugs that are both safe and effective for treating patients with hypertension and those with established vascular disease, including coronary heart disease, cerebrovascular disease, diabetes and progressive renal disease. These five drug groups are diuretics, β-blockers, ACE inhibitors, ARBs and CCBs.
- The major benefit derived from using these five groups of drugs stems from their common actions in lowering blood pressure rather than from particular class-specific effects on other aspects of cardiovascular function. Thus, the ALLHAT trial was not able to differentiate between diuretics, ACE inhibitors, CCBs and even α-blockers in their effects on a primary composite endpoint of fatal and non-fatal myocardial infarction, nor in their effects on all-cause mortality.[4] In the same way, the meta-analysis in 2000 by the Blood Pressure Lowering Treatment Trialists' Collaboration could not differentiate between the effects of "conventional treatment" with diuretics and/or β-blockers and ACE inhibitors or CCBs, on "major cardiovascular events" (a composite endpoint combining stroke, myocardial infarction, heart failure and vascular death).[3] The next analysis from this collaboration, due to be published this year, will have much greater power to differentiate between drug classes, but perusal of the evidence suggests that it will confirm this broad equivalence in reducing overall cardiovascular risk.
- The only differences between the effects of the different drugs reside, or potentially reside, in cause-specific effects on outcomes such as myocardial infarction, stroke, and heart failure. Even here, it is clear that most differences that may emerge, if any do, will be moderate and of the order of around no more than 8%–12%. The one exception is for prevention of heart failure, where the evidence is very clear — calcium antagonists confer no benefit and may have a deleterious effect, and diuretics and ACE inhibitors are clearly superior by a margin of between a quarter and a third. The same holds true for α-blockers, for which the only major comparative study (ALLHAT[4]) terminated the doxazosin comparison with chlorthalidone early because of a doubling in the rate of heart failure compared with diuretics.[21]

When all the available evidence is pooled in the next analysis from the Blood Pressure Lowering Treatment Trialists' Collaboration, some drug groups may be shown to prevent stroke more effectively than others. It seems possible

1: Principles of management

Thresholds for initiation of drug therapy

Low-risk patients with hypertension (minimal elevation of blood pressure; no other risk factors)
- Begin with lifestyle measures
- Start drug therapy if blood pressure is still over 140/90 mmHg after 6 months

Medium-risk patients with hypertension (moderate or minimal elevation of blood pressure; other risk factors and conditions present)
- Start drug therapy if blood pressure is over 140/90 mmHg

Patients with diabetes, chronic kidney disease, or established vascular disease
- Start drug therapy if blood pressure is in the "pre-hypertensive range" (120–139 mmHg systolic; 80–89 mmHg diastolic)

Goals of therapy

- To address all risk factors and conditions, so as to minimise total cardiovascular risk.

All patients with hypertension
- Reduce blood pressure below 140/90 mmHg

High-risk patients with or without elevated blood pressure
- Aim at blood pressure below 130/80 mmHg in patients with diabetes, chronic kidney disease or established vascular disease.

Tables for stratifying patients according to absolute cardiovascular risk and levels of blood pressure are available.[1,2,6,7]

that CCBs may be slightly superior to ACE inhibitors and even to diuretics, though such margins, even if significant, are likely to be of the order of no more than 10%. It also seems clear that diuretics are superior to α-blockers in preventing stroke by close to 20%,[21] and possibly to ACE inhibitors by a more modest margin of 5%–10%, although this latter result may be more relevant to African Americans than white people.[4] It seems likely that β-blockers are less effective than ARBs in preventing stroke, though this is based on a single study (LIFE[13]) and awaits confirmation.

Another group of studies has highlighted the importance of lowering blood pressure in patients at high risk of adverse cardiovascular events, such as those with established vascular disease or diabetes, whether or not they have hypertension. Thus, it is clear from the HOPE study[11] and the PROGRESS trial[12] that patients with coronary heart disease or cerebrovascular disease derive substantial benefits from treatment with blood-pressure-lowering drugs regardless of whether they have hypertension. A similar pattern is seen in patients with diabetes, in whom treatment with ARBs has reduced the progression of renal disease,[18-20] independent of baseline blood pressure. These results are consistent with the results of major epidemiological studies that have confirmed the continuous nature of the relationships between blood pressure and cardiovascular risk right down into the normotensive range.[24-26]

The evidence on use of blood-pressure-lowering drugs in patients with diabetes, kidney disease or established vascular disease who do not have hypertension is still quite limited, and mainly dependent on randomised studies against placebo. There are few comparative studies in such patients that assess the relative value of different classes of blood-pressure-lowering drugs. It is possible that these are the groups of patients in whom particular groups of drugs may have class-specific actions that are advantageous.

Recommendations for lowering blood pressure in 2003

Risk stratification and the importance of reducing the total cardiovascular risk

It is essential to assess each patient's risk profile to stratify the cardiovascular risk and identify and manage the other major risk factors for cardiovascular disease. These include raised cholesterol levels, obesity and smoking, target organ damage, and associated disorders such as diabetes, renal, coronary and cerebrovascular disease. The use of blood-pressure-lowering drugs should be considered in all patients with diabetes, renal disease or established vascular disease, whether they have hypertension or not. Comprehensive tables are provided in the most recent guidelines, for stratifying patients according to absolute cardiovascular risk and levels of blood pressure.[1,2,6,7]

Lifestyle measures

Instituting lifestyle measures to reduce cardiovascular risk and to lower blood pressure should continue to be the foundation for managing all patients with hypertension, diabetes or established vascular disease. This should include smoking cessation, weight reduction, salt restriction and increasing physical exercise wherever applicable. In some patients with a low risk of adverse cardiovascular events or slight elevation of blood pressure, lifestyle measures alone may achieve the goals of therapy without recourse to treatment with blood-pressure-lowering drugs.

Goals for blood-pressure-lowering therapy

The key to reducing the risk of blood-pressure-related disease is lowering the blood pressure. Therefore, the active implementation of a management plan to achieve a goal blood pressure is the most important part of management, and far more important than the choice of drugs (Box 1). The primary focus should be on reaching the goal for systolic blood pressure, which is generally harder to achieve, but more closely linked to reduction in cardiovascular risk.

Indications for initiating blood-pressure-lowering drug therapy

There is widespread agreement that drugs to lower blood pressure should be used in patients with blood pressure readings persistently higher than 140/90 mmHg, even in low-risk individuals without other risk factors (Box 1). Even more important is the widespread recognition and recommendation that, in high-risk individuals, blood-pressure-lowering therapy should be initiated at pressures in a range

2: Individualisation of therapy

Disorder	Diuretics	β-Blockers	Angiotensin-converting enzyme inhibitors	Angiotensin receptor blockers	Calcium antagonists	Aldosterone antagonists
Isolated systolic hypertension	✓				✓	
After myocardial infarction		✓	✓			✓
Stable angina		✓			✓	
Heart failure	✓	✓	✓	✓		✓
Cerebrovascular disease	✓		✓			
Diabetes	✓	✓	✓	✓	✓	
Chronic kidney disease (especially diabetes)			✓	✓		

Ticks indicate the various classes of drugs that are particularly indicated for the conditions shown. In each case one or more of the classes ticked may be used according to the clinical situation.

3: Effective blood-pressure-lowering drug combinations[2,7,27]

- Diuretics and β-blockers
- Diuretics and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers
- Diuretics and calcium antagonists
- Calcium antagonists and β-blockers
- Calcium antagonists and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers

4: "Take-home messages" for clinicians

- Assess and treat all other risk factors and disorders in each patient so as to reduce total cardiovascular risk, not just blood pressure.
- Pursuing an active blood-pressure-lowering regimen until goal blood pressures are achieved is more important than the choice of drug.
- The choice of drug will often be facilitated by clinical pointers in the individual patient; in the absence of such pointers, start with a low-dose diuretic.
- Combination therapy will be needed in most patients and low-dose diuretics will normally form one element of such a regimen.
- There are five first-line classes of blood-pressure-lowering drugs, all of them safe and effective in reducing cardiovascular morbidity and mortality — diuretics, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and calcium antagonists.

that was previously considered within the "normal range", but that was termed "pre-hypertensive" in the recent JNC VII report[6] (Box 1).

Choice of drugs for initiating therapy

Individualisation of therapy in patients with clinical pointers to particular drug classes

In most patients who need blood-pressure-lowering drugs, the choice of agents to initiate therapy is determined by the clinical profile of the patient. This includes illnesses that mitigate against the choice of some drug classes (eg, asthma and β-blockers), or comorbid conditions such as diabetes or vascular disease that suggest drug classes with particular advantage or compelling evidence of benefit (Box 2). This is particularly true in ageing populations where multiple illnesses are increasingly coexistent.

Other aspects of the patient's profile may also help determine the choice — for example diuretics and CCBs are clearly more effective in African American patients than are ACE inhibitors or β-blockers.[4,6]

Choice of drugs in patients without clinical pointers to particular drug classes

This choice, which often stirs the greatest controversy, has probably been made easier by the results of ALLHAT and by the totality of the evidence now available, which suggests that, in the absence of particular reasons to the contrary, drug therapy should start with a low-dose diuretic.[4,6] This is because, from both the largest study (ALLHAT[4]) and from the most recent meta-analysis conducted by the Blood Pressure Lowering Treatment Trialists' Collaboration,[3] it is clear that diuretics are as effective as any other class of drugs for preventing combined vascular endpoints, and for most cause-specific endpoints such as stroke, heart attack and heart failure.[4,6]

Combination therapy

Around two-thirds of patients will require combination therapy with at least two drugs.[1,2,6,7] Diuretics should normally be one element of combination therapy, and where diuretics have been used to initiate drug therapy, the second drug will be chosen from among the other four groups of first-line agents — ACE inhibitors, ARBs, β-blockers and CCBs. Particularly effective combinations are shown in Box 3. In white or Asian patients, one of the most effective combinations is a diuretic with an ACE inhibitor or an ARB; in African American patients, the combination of a diuretic and a CCB might be preferred. There are few data on which to base recommendations tailored to Torres Strait Islanders or Aboriginal Australians.

It is noteworthy that JNC VII,[6] WHO-ISH 1999[2] and the new European Guidelines,[7] all recommend the use of fixed dose combinations, particularly fixed low-dose combinations, and of long acting, once daily preparations to improve adherence to therapy and diurnal control of blood pressure. JNC VII and the European Guidelines further recommend that fixed dose combinations may be used to initiate therapy.[6,7] JNC VII suggests these be used to initiate therapy when the gap between the patient's blood pressure and goal blood pressure is at least 20/10 mmHg.[6]

An overall approach to managing individual patients with hypertension or with blood-pressure-related disease is proposed in the abstract of this article. "Take-home messages" for the practising doctor are shown in Box 4.

Competing interests

J P C has received travel support and honoraria from Servier, Solvay, Boehringer Ingelheim and Pfizer for speaking at conferences in the past two years, and is the chief investigator of two major studies funded by the pharmaceutical company, Servier. L F A has served on the Advisory Board of Bristol-Myers Squibb International Omapatrilat (Vanlev) within the past two years.

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