Reconsidering antihypertensive choices

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No matter how carefully a choice of a P-drug list is made for any given condition, it remains open to reconsideration whenever any of the factors used to weigh the choice of medicines for the list changes. The most easily accommodated changes are perhaps those related to cost, as this is usually considered last, and weighted as least important. Profound changes in the evidence base for efficacy and/or safety are less common, and require more careful handling. This is certainly the case with the choice of medicines to treat hypertension, and particularly to treat this condition in elderly patients who might also present with co-morbid conditions. For many family practices, such patients would represent the majority of hypertensives under treatment. *(SA Fam Pract 2003;45(2):44-45)*

In rating evidence for efficacy and/or safety, it is customary to give the highest regard to the best level of evidence. While many scoring systems for the level of evidence exist, most would rate systematic reviews of well designed, double-blind, randomised trials where there is homogeneity of results as the highest form of evidence. Homogeneity in this context refers to a lack of worrying variability in the direction of the evidence included in the review – e.g. all the trials included would have rated the agent under consideration as better than placebo, with none showing the opposite result. There are times, though, when the results of a single new trial are so significant that they force practitioners to reconsider the evidence provided by pre-existing systematic reviews. The treatment of hypertension presents one such case.

A Cochrane review of the treatment options for hypertension in the elderly was updated recently, to include evidence up until December 1997.[1] This was a meta-analysis of the results from 15 trials involving a total of 21 908 patients. Each was a randomised trial of at least one-year duration in patients at least 60 years of age, which assessed antihypertensive drug therapy and provided both morbidity and mortality data. The results were also considered in the light of the results provided by 10 previous meta-analyses on the subject. Mulrow *et al* concluded that "the evidence regarding the effectiveness of antihypertensive treatment for elders aged 60 to 80 is strong, consistent and convincing". They considered that the cardiovascular benefits of treatment with low dose diuretics or beta-blockers were clear, whether patients presented with diastolic or isolated systolic hypertension. In addition, the evidence for benefits associated with the use of a long-acting dihydropyridine calcium channel blocker (DHP-CCB) in isolated systolic hypertension was also considered to be clear. This latter evidence was provided by a single trial of nitrendipine use. More common DHP-CCBs on the South African market include nifedipine, amlodipine and isradipine. Evidence for those aged over 85 years and for the frail with "multiple severe competing comorbidities" was less clear. For the endpoint of "coronary heart disease morbidity and mortality" (defined as fatal and non-fatal myocardial infarctions and sudden or rapid cardiac death), the combined results of 9 trials reporting these data revealed that treating 1000 patients for about 5 years would prevent 10 such events (95% CI 4 to 15).

Despite the scale of the data combined, a number of limitations were noted. It was stated, for example, that the prevalence of cardiovascular risk factors, cardiovascular disease and competing co-morbid disease was lower among the trial participants than was known to exist in the general population of hypertensive elderly patients. Of particular note was the concluding comment made by the authors: "Trials that assess ACE inhibitors and that compare antihypertensive agents directly with each other are needed to determine the relative efficacy of the pharmacological treatment choices available". One of the trials identified as expected to provide such evidence was the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Those results are now available, and are of such a nature that they demand that all practitioners reconsider their current medicine choices.[2,3] It is worth noting that the authoritative JNC-VI guidelines also date from 1997, just before recruitment into ALLHAT was completed.[4] What then is ALLHAT, and to what extent has it "overturned the apple-cart"?

ALLHAT was designed first and foremost to determine whether the occurrence of fatal coronary heart disease (CHD) or non-fatal myocardial infarction (MI) was lower for high-risk patients with hypertension treated with a calcium channel blocker (represented by amlodipine, a DHP-CCB), an angiotensin-converting enzyme inhibitor (represented by lisinopril), an alpha-blocker (represented by doxazosin) or a diuretic (represented by chlorthalidone, a thiazide). Men and women aged 55 years or older, with hypertension and at least one additional risk factor for CHD events were included. The risk factors considered were myocardial infarction or stroke in the previous 6 months, demonstrated left ventricular hypertrophy, history of type 2 diabetes, current cigarette smoking, low high-density lipoprotein cholesterol (<0.91

mmol/l) or evidence of other atherosclerotic cardiovascular disease. Patients with pre-existing symptomatic heart failure or known compromised (<35%) left ventricular ejection fraction were excluded. Crucially, the trial was designed to enrol sufficient patients into each group so that, even with dropouts and treatment shifts, an intention-to-treat analysis would provide a statistically significant answer for each of the comparisons required. This trial therefore represents that most rare form of evidence – a head-to-head design in patients representative of real-world practice, using clinically important and not only surrogate endpoints over a long follow-up period (4-8 years). Comparison of patient numbers with those for the previously mentioned meta-analysis is instructive – ALLHAT recruited 42 418 patients, randomised to double-blinded groups of 15 255 (chlorthalidone), 9 048 (amlodipine), 9 054 (lisinopril) and 9 061 (doxazosin). If well designed, a single trial with twice as many participants as the total included in the most recent meta-analysis cannot be ignored.

The first shock was provided in March 2000 when the doxazosin arm was prematurely terminated.[2] Patients on the alpha-blocker showed a 25% higher rate of cardiovascular disease and twice the rate of heart failure than those on the diuretic. The final results, published in December 2002 were no less important. While all three agents lowered blood pressure (a typical surrogate endpoint), the reduction on chlorthalidone was somewhat greater than that with lisinopril. Amlodipine lowered diastolic blood pressure more than chlorthalidone but systolic blood pressure to a lesser extent. By the end of the fifth year of follow-up, the target BP (<140/90 mmHg) was achieved by 68% of those randomised to chlorthalidone, 61% of those on lisinopril and 66% of those on amlodipine. However, for the primary outcome measured – CHD death and non-fatal MI – there was no significant difference between the three groups. For chlorthalidone vs amlodipine the relative risk (RR) was 0.98 (95% CI 0.90-1.07) and for chlorthalidone vs lisinopril the RR was 0.99 (95% CI 0.91-1.08). Chlorthalidone was however superior to amlodipine in preventing heart failure. This efficacy and safety of the thiazide was shown despite the occurrence of predictable metabolic effects on cholesterol, potassium and blood glucose levels. Chlorthalidone's superiority was also demonstrated in both diabetic and non-diabetic patients. There was also evidence of decreased response to the ACE-I in black patients.

The results of ALLHAT stand up to closer scrutiny. The patient groups were essentially matched at the onset, and representative of what might present to a family practice – the mean age was 67 years, 47% were women, 35% black and 36% diabetic. Initial double-masked drugs were presented in identical encapsulated forms, and allowed an equal number of dose titrations (including a sham titration for chlorthalidone). Subsequent addition of open-label Step 2/3 drugs was permitted (using atenolol, reserpine, clonidine or hydralazine). That a diuretic could not be added to the regime for a patient not responding to ACE-I monotherapy was a limitation. Step 2 or 3 drugs were necessary by 5 years in 40.7% of those on chlorthalidone, 39.5% of those on amlodipine and 43.0% of those on lisinopril. Losses to follow-up were minimal. Adverse events were similar, except that more cases of angioedema occurred in the lisinopril group (including one fatal event).

While some might be tempted to claim that these results are only directly applicable to the three drugs tested, the ALLHAT authors dispute this, pointed out that "combined with evidence from other trials, we infer that the findings also broadly apply to the drug classes ... that the study drugs represent", the only *caveat* being that extrapolation to non-dihydropyridine CCBs is probably not justified. Perhaps the best encapsulation of the results was provided in the accompanying JAMA editorial "the ALLHAT results ... are particularly noteworthy, because there is no cost-quality trade-off; the most effective therapy was also the least expensive".[5] Appel agrees that "for ACE inhibitors, there is no compelling reason to believe that any one ACE inhibitor is superior", but expresses some concern that chlorthalidone is well used in trials (and shown to be effective), but seldom used in clinical practice.

The ALLHAT authors also cited a study in the US that showed how diuretic use had declined from 56% of hypertension prescriptions in 1982 to only 27% in 1992, accounting for an increased expenditure of US$3.1 billion per year (the total antihypertensive drug spend being estimated at US$15.5 billion per year in 2002).[6] There is no reason to believe that the South African market is any different, with increasing use of newer, more expensive agents over time. While ALLHAT provides no data on some of the newer groups – such as the angiotensin receptor blockers – the evidence bar has been immeasurably raised. Future policy changes and practitioners' P-drug choices must first address the question posed by ALLHAT – "Are newer types of antihypertensives, which are currently more costly, as good or better than diuretics in reducing CHD incidence and progression?". Considerable evidence will be necessary to provide a different answer to that now known – low-dose thiazide diuretics are the initial treatment of choice for hypertension, even in elderly patients with co-morbid conditions such as type 2 diabetes and in black patients.

One last issue deserves attention. A BMJ commentary has noted that sales of doxazosin remained virtually constant (at about US$800 million worldwide) after the cessation of the alpha-blocker arm in 2000.[7] A similar "damage control" strategy from pharmaceutical marketing departments can be expected in response to the latest ALLHAT results. Equally, aggressive marketing of appropriate low-dose thiazide diuretics is not expected. In some markets, access to stand-alone thiazides is increasingly difficult. The BMJ commentary ends with this thought-provoking quote "When dealing with interventions whose marginal benefit comes at substantial cost – both economic and medical – we have to ask not only how much we are willing to spend for a tiny potential gain, but also what we sacrifice in the name of such a gain. Inevitably, when we spend dollars on extremely expensive medicines we take those dollars from less sexy but much more important public health interventions. Ultimately we abdicate our responsibility, as well as risk the public health, if we allow proprietary companies, whose primary interest has to be selling their wares, to guard the public hen house". Bearing the results of this landmark head-to-head trial in mind when faced with a deluge of placebo-controlled trials of newer agents, often measuring surrogate outcomes, will be an important part of ensuring the quality use of medicine in this very prevalent condition.❐

References available on request.