

Hypertension

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Introduction

Hypertension is a rapidly moving clinical field with frequent developments in new pharmacologic agents and management strategies. Perhaps more importantly, there have been substantial improvements in our understanding of how best to use the drugs available to us. In this article, I will review some of the more important advances in our understanding of hypertension over the past two years, specifically by reviewing six important trials, one survey and two sets of guidelines, all published between January 2002 and June 2004.

ARB – a better blood-pressure drug

A huge study (LIFE), involving more than 800 clinical centres in Scandinavia, the UK and USA, compared the angiotensin receptor blocker (ARB) losartan and the beta-blocker atenolol as part of treatment for people with high BP (sitting BP, 160-200/95-115 mmHg) and left ventricular hypertrophy (LVH ascertained by electrocardiography).^{1,3} This double-blind trial looked at 9193 patients aged 55 to 80 years; 54% were female, 92% white, 13% diabetic, and 8 and 16% having a history of cerebrovascular and coronary artery disease respectively. BP at baseline was closely matched, and at the end of the study, it was reduced by 30.2 / 16.6 mmHg in the losartan group and 29.1 / 16.8 mmHg in the atenolol group. More than half of both groups received concomitant hydrochlorothiazides and other antihypertensive agents as needed to achieve goal BP of less than 140/90 mmHg. Mean daily doses for losartan and atenolol were 82 mg and 79 mg respectively. During follow-up (mean, 4.8 years), after adjusting for differences in achieved BP levels, the incidence of the primary composite end-point

(cardiovascular death, myocardial infarction - MI, or stroke) was lower with losartan than atenolol (11% vs 13%, $P = 0.021$). Most of the benefit was driven by a 25% reduction in the risk of fatal and non-fatal stroke ($P = 0.001$), with no benefit seen for fatal or non-fatal MI, cardiovascular death and all-cause mortality. Moreover, new-onset diabetes was less common (25% reduction) with losartan. In addition, losartan was better tolerated and caused greater regression of ECG-LVH than atenolol. LIFE also looked at two prespecified groups: patients with diabetes and patients with isolated systolic hypertension. In diabetics ($n = 1195$), losartan fared significantly better than atenolol regarding the primary composite end-point ($p = 0.03$), all-cause mortality ($p = 0.002$), cardiovascular mortality ($p = 0.028$), and admission for heart failure ($P = 0.019$). MI and stroke rates were not different between the two treatment arms in diabetics. In patients with isolated systolic hypertension ($n = 1326$), losartan also reduced the rate of stroke and cardiovascular deaths more than did atenolol.

In summary, these studies demonstrate that angiotensin-receptor blockade is more effective and better tolerated than beta-adrenergic receptor blockade for the treatment of hypertension in the high-risk group of patients with LVH.

Diuretics best for high blood pressure

The largest hypertension clinical trial ever conducted (ALLHAT) was a randomised, double-blind trial designed to compare the rate of coronary heart disease (CHD) events in 'high-risk' hypertensive patients initially randomized to a diuretic (chlorthalidone) vs each of three 'alternative' antihypertensive drugs: an alpha-adrenergic blocker (doxazosin), an ACE-inhibitor (lisinopril) and a calcium-channel blocker (CCB) (amlodipine), as well as the effects of lipid lowering therapy in these individuals.⁴ Eligible patients were aged 55 years or over with hypertension and with at least one other CHD risk factor (previous MI or stroke, LVH by ECG or echocardiogram, diabetes mellitus, current cigarette smoking, and low HDL cholesterol levels). The original trial population comprised of 42,418 patients, but the doxazosin arm of the trial was stopped prematurely in January 2000 because of a 25% higher rate of combined cardiovascular events and a twofold higher rate of admission for heart failure (HF) compared with chlorthalidone. The remaining 33,357 patients stayed on their study drugs until the end of the study. Of these, 15,255 were randomized to chlorthalidone (12.5 – 25.0 mg/day), 9048 to amlodipine (2.5 – 10.0 mg/day), and 9054 to lisinopril (10-40

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mg/day). If BP was not controlled to below 140/90 mmHg after dose optimization with the study drug, open-label drugs (atenolol, clonidine or reserpine as step 2 and hydrallazine as step 3) could be added at the physician's discretion. The mean age of participants was 67 years; 47% were women, 35% were black and 36% were diabetic. After a mean follow-up of 4.9 years, primary outcome (fatal CHD and non-fatal MI) events occurred in 2956 patients, with virtually identical frequencies in each of the three treatment groups (6-year rates of 11.5%, 11.4% and 11.3% in the diuretic, ACE inhibitor and CCB respectively). Likewise, all-cause mortality was not different between the three groups. Differences were noted in secondary outcomes however. Compared with those taking chlorthalidone, patients on amlodipine had on average 0.8 mmHg higher systolic BP, 38% higher risk of developing HF ($P < 0.001$), and 35% higher risk of hospitalization or fatal HF ($P < 0.001$). Interestingly, lisinopril appeared to be worse than chlorthalidone – those taking lisinopril had on average about a 2 mmHg higher follow-up systolic BP, 15% higher risk of stroke ($P < 0.02$), and a higher risk of combined cardiovascular disease ($p < 0.001$) with 11% higher risk of hospitalization or treated angina ($P = 0.01\%$) as well as 10% higher risk of coronary revascularization ($P = 0.05$). Rather surprisingly, patients on lisinopril also had a 19% higher risk of developing HF ($P < 0.001$).

In summary, thiazide-type diuretics are superior to ACE-inhibitors or CCBs in preventing major cardiovascular disease events. They are also less expensive. Therefore, thiazide diuretics should be preferred first-line treatment for hypertension, if BP control is inadequate after first-line treatment with another agent, a thiazide should be the preferred second step.

Study clouds hypertension drug debate

The ANBP2 (Australian National Blood Pressure Study - 2) appeared to contradict the above-mentioned ALLHAT trial.⁵ This open-label trial enrolled 6083 patients (51% female) aged 64 to 84 years, with hypertension being treated by family practitioners. Overall, participants in ANBP-2 were more active and had fewer major risk factors for CHD than the ALLHAT population. Patients received either a diuretic or an ACE inhibitor as the initial recommended drug; the choice of the specific agent and dose was made by the family practitioners. At the end of the five-year study period, BP had decreased by 26/12 mmHg from baseline in each group. 58% of patients randomly assigned to the ACE-inhibitor group and 62% of those assigned to the diuretics group were still receiving the assigned treatment. The rate of the composite outcome (all cardiovascular events and all-cause mortality per 1000 patient-years) was lower in patients among patients on ACE-inhibitors (56.1) than in those who were allocated to the diuretics group (59.8) ($P = 0.05$). The difference in outcome was most pronounced among elderly men. Overall rates of CHD, stroke and HF were the same in both groups.

In summary, an ACE-inhibitor was more effective than a thiazide diuretic in this active, elderly population. In an editorial

accompanying the study, it was pointed out that the apparently contradictory findings from the ALLHAT trial might be explained by ethnic differences among the two study populations. Whites made up 95% of the Australian study group whereas 35% of ALLHAT participants were blacks. Blacks are known to respond better to diuretics than other classes of hypertension drugs. One should also note that the rate of abandoning allocated therapy in the ANBP2 study was quite large (about 30% in each group).

Don't forget lifestyle recommendations

In the PREMIER trial⁶, the question was: In persons with above-optimal BP, what is the relative effectiveness of two behavioral interventions (established lifestyle recommendations [ELR] and ELR plus the Dietary Approaches to Stop Hypertension [DASH] diet) compared with advice only? ELR meant weight loss for overweight participants, reduced sodium intake, increased physical activity, and limited alcohol intake. The DASH diet meant reduced fat and cholesterol and increased potassium, calcium, magnesium, protein and fibre through consumption of fruit, vegetables and low-fat dairy products. 810 generally healthy adults were recruited from four clinical centres in the US. Mean age was 50 years, 62% were women, and all had above-optimal BP (mean systolic BP 120-159 mmHg and diastolic BP 80-95 mmHg during three screening visits). Exclusion criteria were use of drugs affecting BP, target organ damage, diabetes, previous cardiovascular event, cancer and pregnancy. The ELR and the ELR+DASH groups had 14 group meetings and 4 individual counseling sessions during the initial six months. Patients in the advice group had a single 30-minute individual session with a dietician. With regards to outcome, patients in the behavioral intervention groups had significantly greater reductions in systolic and diastolic BP than did patients in the advice group. For example, mean between-group differences in systolic BP were -3.7mmHg (ELR vs advice) and -4.3mmHg (ELR + DASH vs advice).

In summary the nonsignificant differences between the behavioral groups suggest that clinicians should focus on promoting weight loss (averaged 5 kg in the study) through caloric restriction and exercise: lifestyle measures, primarily weight loss, lowers blood pressure.

A third of American adults have high blood pressure

In an update of the National Health and Nutrition Examination Survey (NHANES), researchers noted the first overall increase in hypertension disease prevalence - 4% - after three decades of declining rates.⁷ Overall, almost a third (29%) of the study participants were hypertensive – defined as having a BP of 140/90 or higher or reported use of antihypertensive drugs. In both past NHANES studies, the prevalence rate was 25%. Based on data from nearly 5500 Americans over age 18 examined from 1999 to 2000, researchers made estimates on how BP affected the general population. Data was compared

with previous NHANES studies involving some 9,900 people in 1988-1991 and 9,700 in 1991-1994. Other survey findings included an increase in disease rates in seniors of nearly 8% such that now, two out of three of those over age 60 have high BP compared with 58% in 1988. Regarding ethnic groups, about 34 % of blacks were afflicted, compared with 29% of whites and 21% of Hispanics. About 30% of people with high BP were unaware of their hypertension and 42% of people in the study with high blood pressure were not being treated for it.

In summary, contrary to early reports, hypertension prevalence is increasing in the US. Hypertension control rates, although improving, continue to be low. Programmes targeting hypertension prevention and treatment remain of utmost importance.

The new normal in high blood pressure

New USA federal guidelines on high blood pressure defined a new prehypertension category defined as systolic BP 120 – 139 mmHg or diastolic BP 80 –89 mmHg.⁸ The new category includes about 45 million people (22% or nearly 1 in 4 adults in the USA) who once thought they had normal BP and who now, based on the JNC 7 report, are being urged to make lifestyle modifications to lower or prevent BP. The guidelines quote research that show that by the age of 55 years, men and women who do not already have high BP have a 90% chance of developing it later. Systolic hypertension is recognized as a more important cardiovascular risk factor than its diastolic counterpart in those aged 50 years or older. In addition, the risk of death due to MI and stroke increases rapidly with rising BP levels, starting at levels as low as 115/75 mmHg. For every 20/10 mmHg rise in BP above this level, the risk of death from cardiovascular disease doubles. The new guidelines state that diuretics should be used as first-line treatment for most people with high BP without other risk factors such as heart failure, history of MI, diabetes, or kidney disease. The report calls for more aggressive treatment of the condition through the use of a combination of BP lowering medications; acknowledges that most people with hypertension will require two or more drugs to achieve goal BP of 140/90 or less, and exhorts that the goal BP in people with kidney disease and diabetes should be less than 130/80 mmHg.

The importance of overall cardiovascular risk assessment

The new European guidelines (ESH-ESC) guidelines have retained previous cut-off levels to define various grades of hypertension, but emphasize that the real threshold for hypertension depends on an individual patient's total cardiovascular risk profile. The guidelines explain how to assess a patient's risk according to the presence or absence of additional risk factors, such as target-organ damage, and provide an algorithm for the initiation of treatment.⁹ According to the guidelines, full assessment of cardiovascular risk would require formal diagnosis, after at least three separate BP measurements,

an ECG, measurement of abdominal circumference, plasma creatinine, lipids, glucose and using a high-sensitivity assay, C-reactive protein. In contrast with JNC 7, the European guidelines do not use the term prehypertension, although they identify BP in the range of 130-9/85-9 mmHg as 'high normal' BP. The report then recommends that people with 'high normal' BP initiate lifestyle measures, have other risk factors corrected and, if cardiovascular risk is high, start antihypertensive treatment. This approach is consistent with that recommended in the JNC 7 indicating that this difference relates more to style than substance. The European guidelines categorize the BP in the range 120-9/81-4 mmHg as normal though not optimal. Therefore, it is really within these values that the approach to BP classification differs across the Atlantic. Therapy should be initiated either with a low dose of a single drug or a low-dose combination of two drugs. The guidelines point out that, in general, the five main classes of antihypertensive drugs (diuretics, beta blockers, CCBs, ACE-inhibitors, and ARBs) are all suitable for initiating and maintain therapy, except in certain defined conditions, favouring or contraindicating use. For example, ACE-inhibitors are favoured for use in post-MI, heart failure, left ventricular dysfunction, nondiabetic and diabetic nephropathy, and proteinuria,

Calcium channel blocker or beta blocker in hypertensive CAD?

In a large 14-country open-label trial, called INVEST, 22,576 patients with hypertension and coronary artery disease, aged 50 years or older, were assigned either a CCB (sustained-release verapamil) or a beta-blocker (atenolol).¹⁰ If needed, the ACE-inhibitor trandolapril and hydrochlorothiazide were added (in that order) in the verapamil group, and hydrochlorothiazide and trandolapril were added (in that order) in the atenolol group. However, the ACE-inhibitor was added immediately for patients in both groups who had diabetes, renal impairment or heart failure. At 24 months, most patients in both groups were receiving ACE-inhibitors, and half were receiving at least three hypertension drugs. During a mean follow-up of 2.7 years, no differences were found between the two groups in a combined endpoint (death, nonfatal MI, or nonfatal stroke) or in any individual endpoints. BP control and side effect profiles were similar in the two groups. In summary, in patients with coronary artery disease and hypertension, initial therapy with a CCB or with a beta-blocker yielded similar outcomes.

The case for aggressive initial therapy

The VALUE study was designed to determine whether, for the same level of BP reduction, valsartan, an ARB, would be more cardioprotective than the CCB, amlodipine.¹¹ In this large trial, 15,245 hypertensive patients aged 50 years or older at risk for cardiovascular complications were randomized into either the CCB-based or the ARB-based regimens. Mean age was 67.2 years, 32% were diabetic, 46% had a history of coronary artery disease and 20% had a history of cerebrovascular disease.

Patients were randomized to once daily treatment with valsartan 80 mg or amlodipine 5 mg, titrated to 160mg or 10 mg respectively. If not at goal BP, hydrochlorothiazide was added first at 12.5mg then at 25 mg. While the VALUE trial demonstrated better BP control compared to other large scale studies, 40% of patients in this high risk population did not achieve the predefined BP goal of 140/90 mmHg or less. With respect to the incidence of the primary endpoint of cardiac mortality and morbidity, there was no difference ($p = 0.81$) between valsartan (10.6%) and amlodipine (10.4%). Likewise, all-cause death rates were similar (11% valsartan versus 10.8% amlodipine; $p = 0.45$). The two treatment regimens effectively lowered BP but unintentionally, early in the trial, BP was lowered more with amlodipine than with valsartan. These unintended differences in BP made interpretation of the secondary endpoints difficult. For example, the rate of MI was 4.8% with valsartan versus 4.1% with amlodipine ($p = 0.02$). The rate of hospitalization for HF with valsartan was less than with amlodipine. Of importance, there was a 23% risk reduction in new-onset diabetes with the ARB (13.1% incidence with valsartan, 16.4% with amlodipine, $p < 0.00001$). This finding confirmed the observation from the LIFE studies that ARBs are associated with a reduction in new-onset diabetes.

In summary, despite the equivalency of the primary endpoint, VALUE clearly showed the importance of aggressive initial antihypertensive therapy, with study data showing achieved BP at 1 month and 6 months was predictive of future cardiovascular events.

Conclusions

Effective lowering of blood pressure causes a highly significant risk reduction for stroke and CHD. All scientific evidence favours an aggressive approach to treating hypertensive patients. In the megatrials LIFE, ALLHAT, ANBP-2, VALUE, HOPE¹² and the cardiological trial EUROPA,¹³ large reductions in event rates were seen with relatively small BP reductions. Quite simply, *the lower the blood pressure, the better the prognosis*, just as holds true for cholesterol levels. With regards to application of guidelines, I favour the definition of hypertension from JNC 7, adding the risk profiling set out by the ESH-ESC guidelines, and leaving the drug selection to the physician. Despite the recommendation of the JNC 7 guidelines to initiate therapy with a thiazide diuretic, it is worth noting that much of this recommendation was based on analysis of secondary endpoints (considered soft data) in ALLHAT. To my mind, ACE-inhibitors and ARBs are at least as equally effective as the other classes of antihypertensive drugs on major cardiovascular events and, furthermore, appear to have benefits beyond BP lowering. However, it appears that these drugs acting on the RAS lower the BP more slowly, and therefore adding a diuretic very early on is probably indicated. Ultimately, however, only a thorough and comprehensive assessment of a drug's risk and benefits in a given patient will allow us to optimize the treatment of hypertensive cardiovascular disease.

References

1. Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359:995-1003
2. Lindholm LH, Ibsen H, Dahlöf B, et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359:1004-10
3. Kjeldsen SE, Dahlöf, Devereux RB et al. Effects of losartan on cardiovascular morbidity and mortality in patients with isolated systolic hypertension and left ventricular hypertrophy: a Losartan Intervention for Endpoint Reduction (LIFE) substudy. *JAMA*. 2002;288:1491-8
4. ALLHAT Officers and Coordinators for the ALLHAT Cooperative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288:2981-97
5. Wing LM, Reid CM, Ryan P, et al. A comparison of outcomes with angiotensin-converting enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med*. 2003;348:583-92
6. Appel LJ, Champagne CM, Harsha DW, et al. Effect of comprehensive lifestyle modification on blood pressure control: main results of the PREMIER clinical trial. *JAMA*. 2003;289:2083-93
7. Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988-2000. *JAMA*. 2003;290:199-206
8. Chobanian AV, Bakris GL, Black HR et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560-72
9. 2003 European Society of Hypertension – European Society of Cardiology Guidelines for the management of arterial hypertension. *J Hypertens* 2003; 21: 1011-1053
10. Pepine CJ, Handberg EM, Cooper-DeHoff RM et al. A Calcium Antagonist vs a Non-Calcium Antagonist Hypertension Treatment Strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): A randomised controlled trial. *JAMA*. 2003;290:2805-16
11. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) randomised trial. *Lancet*. 2004;363:2022-31
12. The Heart Outcomes Prevention Evaluation (HOPE) Study investigators. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med*. 2000;342:145-53. [Errata, *N Engl J Med* 2000;342:748,1376.]
13. European trial On reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled multicentre trial (the EUROPA study). *Lancet*. 2003;362:782-788