MEDICAL UPDATE

Hypertension Update: Lessons from the Literature

H T Ong, FRCP

Consultant Cardiologist & Physician, H T Ong Heart Clinic, 251-C Burmah Road, 10350 Penang

Our concept of hypertension has changed significantly over the last decade and the JNC VI[1] and the WHO-ISH[2] guidelines have institutionalize many of the newer ideas on hypertension. Nevertheless, there have been several large studies reported since then so that it is easy to be overwhelmed by this deluge of information. It is important for the non specialist to extract a few important practical lessons from all these data, so as not to miss the forest for the trees and better manage this modern challenge of controlling hypertension.

Lesson 1: Systolic hypertension is pathological and is a more important predictor of adverse cardiovascular events than diastolic hypertension.

It was not so long ago that doctors believed that blood pressure naturally rises with age and that systolic elevation of blood pressure, especially in the elderly, was benign. The first major trial to demonstrate the value of treating systolic hypertension was the SHEP[3] study reported in 1991. In March 2000, Staessen reported on a meta-analysis of eight trials on isolated systolic hypertension totaling 15,693 patients[4]. All patients were above 60 years of age, had a systolic blood pressure above 160 mmHg and a diastolic blood pressure below 95 mmHg, and were followed for a median of 3.8 years. Treatment was found to reduce total mortality by 13%, cardiovascular mortality by 18%, strokes by 30% and coronary events by 23%, all of which were highly significant statistically. Treatment was specially effective in men, in those above 70, in those with prior cardiovascular complications and in those with a wide pulse pressure. It was also found that there was no J curve phenomenon and further lowering of the normal diastolic blood pressure in these patients did not produce harm.

In May 2001, the Cardiovascular Health Study was reported[5]. This was a Population-based study of 5888 healthy adults aged above 65 years. They were examined at baseline and all cardiovascular events were noted during follow-up, which averaged 6.7 years. It was found that systolic blood pressure, diastolic blood pressure and pulse pressure were associated with myocardial infarction and stroke, but systolic blood pressure was a better predictor of cardiovascular events than diastolic blood pressure or pulse pressure The association was linear and no J shaped relationship was noted.

Although most of the data on pathology of systolic hypertension relates to older patients, there is also good evidence for the association between systolic blood pressure and cardiovascular disease in the younger group. The Chicago Heart Association Detection Project in Industry was reported in June 2001[6]. This study assessed the relationship of blood Pressure to

This article was accepted: 15 June 2002
Corresponding Author: H T Ong, H T Ong Heart Clinic, 251C Burmah Road, 10350 Penang

cardiovascular events over a 25-year period amongst 10,874 young men aged 18 to 39 at baseline. The association of systolic blood pressure to coronary heart disease mortality was continuous and graded. Again, systolic blood pressure was a stronger predictor of coronary heart disease mortality (hazard ratio 1.26 for 1SD higher SBP) than diastolic blood pressure (hazard ratio 1.17 for 1SD higher DBP). The conclusion of this large study was that elevated blood pressure was significantly related to increased mortality from coronary heart disease, cardiovascular heart disease and all causes.

Lesson 2: We should aim to normalize and optimize blood pressure, especially in diabetic and high-risk patients.

There have been two often-quoted trials that directly addressed the question of target blood pressure to aim for in treating hypertensives. The UKPDS 38[7] was part of the large UKPDS study on diabetic patients, and 114[8] diabetics who were also hypertensives were put into either a tight blood pressure control group, or a conventional blood pressure control group. Therapy was with captopril or atenolol with the addition of other agents as required. Mean blood pressure at entry was 160/94 mmHg, and follow-up was over 8.4 years. The tight control group achieved a mean blood pressure of 144/82 mmHg, while the conventional control group achieved a mean blood pressure of 154/87 mmHg. Strokes, microvascular disease, deaths related to diabetes and any diabetic related end-point were all significantly lower in the tight blood pressure control group. The conclusion was that tight blood pressure control in diabetic hypertensives produced lower mortality and morbidity rates. The other major trial, the HOT study[8], was a large study of 18,790 patients aged 50-80 years with a diastolic blood pressure between 100 to 115 mmHg. The aim was to treat to one of three target diastolic blood pressure, ≤90mmHg, ≤85 mmHg or ≤80 mmHg, using felodipine with the addition of other agents as appropriate. After an average follow-up of 3.8 years, mean achieved blood pressure was 85.2 mmHg, 83.2 mmHg and 81.1 mmHg in the three groups. There was no significant difference in the incidence of major cardiovascular events, myocardial infarction, stroke, cardiovascular mortality or all cause mortality in the three target blood pressure groups. However, amongst diabetic patients (n=1501), major cardiovascular events and cardiovascular mortality were significantly lower in the lowest target diastolic blood pressure group. In 3080 patients with prior ischemic heart disease, there was a significant reduction of strokes in the group treated to the lowest blood pressure target. The findings support the contention of intensive lowering of blood pressure in diabetics and others at special high risk of further cardiovascular events.

Both the JNC VI1 and the WHO-ISH2 define blood pressure categories as follows:

	Systolic (mmHg)	Diastolic (mmHg)
Optimal	<120	<80
Normal	<130	<85
High-norma	130-139	85-89
Hypertension	≥ 140	≥ 90

More recently, follow-up of the Framingham Heart Study averaging over 11 years found that risks for cardiovascular events rose progressively from optimal to high-normal in both men and women[9]. In the PROGRESS study, patients considered normotensive with a blood pressure below 160/90 mmHg who had a prior stroke or transient ischemic attack, saw a significant reduction in stroke and major vascular events with anti-hypertensive treatment[10]. In fact, it was the patients put on a combination therapy with an angiotensin converting enzyme inhibitor (ACEI) and diuretic who showed a significant reduction in strokes, not seen in the group on monotherapy with the ACEI. This further adds to the evidence that our previous definition of normotension was too high and we should seek to treat aggressively to normalize and optimize blood pressure in hypertensive patients, regardless of age, especially if they be at high risk of cardiovascular events.

Lesson 3: Beta-blockers (BB), diuretics (D), angiotensin converting enzyme inhibitors (ACEI), angiotensin-receptor blocker (ARB) and calcium antagonists (CA) have all been shown to reduce adverse events in hypertensive therapy. A combination of drugs is often needed to achieve appropriately low blood pressure levels.

It is good to recall that hypertension is an asymptomatic condition that brings morbidity and mortality because of the onset of its complications. The available evidence from large-scale meta-analyses shows that regardless of agents, it is blood pressure reduction that will result in a reduction of the complications of hypertension[11, 12]. To reach the blood pressure targets suggested, a combination of agents is required[13]. The practical lesson must surely be to concentrate on achieving adequate blood pressure control, to combine agents as needed and not to be confused by ongoing debate about superiority of different agents. Different patients will have different tolerance to the adverse effects of different agents, costs vary, and these personal factors play a very important role in deciding drug choice.

Since hypertension causes no symptoms, drug therapy must not have significant adverse effects which can reduce quality of life and so promote non-compliance. CA and ARB generally have few adverse effects. There can be no doubt that short acting dihydropyridine CA should no longer be used, although the long-acting forms are as good therapeutically as other agents[14]. There is evidence that CA are especially valuable in the prevention of strokes and dementia[12, 15, 16]. The ARB have recently been shown to be of special value in type II diabetic patients with hypertension, retarding deterioration of renal function and reducing adverse cardiovascular events more effectively than their comparative agents[17, 18].

The presence of concomitant disease or complications will guide the choice of agent for hypertension control. ACEI are accepted agents for symptomatic and prognostic treatment of heart failure. They also reduce cardiovascular events in coronary and other high-risk patients, seemingly in excess of the blood pressure lowering effect[19]. Thus hypertensive patients with heart failure or at special risk of cardiovascular pathology will benefit from having an ACEI included in their therapy. Alpha-blockers will aid the patient with prostatism. Diuretics will symptomatically benefit the patient with heart failure. Beta-blockers are valuable in ischemic heart disease, symptomatically and prognostically. Beta-blockers and diuretics have become the gold standard against which other anti-hypertensives are gauged[20]. Given their very long history of safe use, the low cost and proven efficacy, they should be considered for use when no contraindication exists.

The practicing physician has a difficult task today deciding on important pointers in the face of a glut of data and studies, some of which seem to contradict each other. It is important to try to be objective, to view reports with an open and alert mind, and to look for proof from a variety of sources. Most importantly, we must not be resistant to change and new information. Recent reports that uncontrolled and undiagnosed hypertension occurs because physicians are not applying recent guidelines and holding onto outmoded ideas reflects a need for continued emphasis in this important area[21, 22].

References

1. Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. The Sixth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. Arch Intern Med 1997; 157: 2413-46.
2. Guidelines Subcommittee. 1999 World Health Organisation-International Society of Hypertension guidelines for the management of hypertension. J Hypertens 1999; 17: 151-85.
3. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA; 265: 3255-64.
4. Staessen JA, Gasowski J, Wang JG, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. Lancet 2000; 355: 865-72.
5. Psaty BM, Furberg CD, Kuller LH et al. Association between blood pressure level and the risk of myocardial infarction, stroke and total mortality. The Cardiovascular Health Study. Arch Intern Med 2001; 161: 1183-92.
6. Miura K, Daviglus ML, Dyer AL, et al. Relationship of blood pressure to 25-year mortality due to coronary heart disease, cardiovascular diseases, and all causes in young adult men. The Chicago Heart Association Detection Project in Industry. Arch Intern Med 2001; 161: 1501-08.
7. UK prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998; 317: 703-13.
8. Hansson L, Zanchetti A, Carruthers, et al. Effects of intensive blood pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. Lancet 1998.
9. Vasan RS, Larson MG, Leip EP, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. N Engl J Med 2001; 345: 1291-7.
10. PROGRESS Collaborative Group. Randomized trial of a perindopril-based blood pressure lowering regimen among 6105 individuals with previous stroke or transient ischemic attack. Lancet 2001; 358: 1033-41.
11. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood pressure lowering drugs: results of prospectively designed overviews of randomized trials. Lancet 2000; 355: 1955-64.
12. Staessen JA, Wang JG, Thijs LT. Cardiovascular protection and blood pressure reduction: a meta-analysis. Lancet 2001; 358: 1305-15.
13. He J, Whelton PK. Selection of initial antihypertensive drug therapy. Lancet 2000; 356: 1942-43.
14. Brown MJ, Palmer CR, Castaigne A, de Leeuw PW, et al. Morbidity and mortality in patients randomized to double-blind treatment with long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS Study: Intervention

as a goal in Hypertension Treatment (INSIGHT). Lancet 2000; 356: 366-72.

15. Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomized double-blind placebo controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet 1998; 352: 1347-51.
16. Opie LH, Schall R. Evidence-based evaluation of calcium channel blockers for hypertension: equality of mortality and cardiovascular risk relative to conventional therapy. J Am Coll Cardiol 2002; 39: 315-22.
17. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. New Engl J Med 2001; 345: 851-60.
18. Lindholm LH, Ibsen H, Dahloff B, et al, for the LIFE study group. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. Lancet 2002; 359: 1004-10.
19. Heart Outcomes Prevention Evaluation 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.
20. Hasson L, Lindholm LH, Ekbom T, et al. Randomized trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension 2 (STOP- Hypertension 2) study. Lancet 1999; 354: 1751-56.
21. Hyman DJ, Pavlik VN. Characteristics of patients with uncontrolled hypertension in the United States. New Engl J Med 2001; 345: 479-86.
22. Oliveria SA, Lapuerta P, McCarthy BD, L'Italien GJ, Berlowitz DR, Asch SM. Physician related barriers to the effective management of uncontrolled hypertension. Arch Intern Med 2002; 162: 413-20.