Prospects for hypertension in the next decade

During the second half of the twentieth century our knowledge of the aetiology of and pathophysiological mechanisms underlying hypertension have advanced immeasurably. Furthermore, few, if any, areas of medicine have as many major morbidity and mortality trials to inform optimal management as does hypertension.

Nevertheless, despite having the results of these major trials[1] – many of which have been published in the last decade – the answers to most of the outstanding questions which prevailed before the last decade remain unresolved (see table 1). Prospects for answering some of these outstanding questions are discussed below.

'Answers to most of the outstanding questions which prevailed before the last decade remain unresolved'

Neil Poulter
President, BHS

Establishing optimal first-line therapy

Despite the largest of all hypertension trials – ALLHAT[2], which was designed to determine the optimal first-line therapy – confusion remains reflecting, in part, the difficulties of this trial.[3] In light of ALLHAT, guidance from JNC VII[4] recommends the use of thiazide-like diuretics for most patients. Whilst it seems reasonable to recommend low-dose diuretics as a starting point for many patients, the trial evidence for using genuinely low-dose thiazides in this context[5] is by no means compelling except for cost reasons. Furthermore, it is inherently unlikely, given the heterogeneity of the hypertensive population, that any one drug is the best for all subgroups and types of patient.

Meanwhile there is a continuing need for more effective agents from among currently available drug classes – ideally with fewer side effects. Perhaps, more importantly, newer classes of agents are required and several new classes of agents are being developed. To provide real advances over currently available agents, such products will be required to have long duration of action and low side-effect rates, with blood pressure (BP) lowering efficacy associated with commensurate reduction in cardiovascular events. The benefits of pharmacogenetics, whereby drugs may be targeted on the basis of genetic profiling, are considered by some to be on the horizon – others believe this to be a very distant prospect. Whatever advances in new therapies emerge, it is increasingly clear that if current BP targets are to be reached, the majority of patients will require more than one drug and so the issue of optimal first-line therapy is yesterday's question for most patients. Consequently, activity aimed at answering this question should be limited in the next decade.

Establishing optimal combination therapy

As BP targets are set lower and lower with successive sets of management guidelines, practice will have to move towards the use of two or more drugs to lower BP sufficiently. This is likely to drive a move towards the increasing use of fixed combination therapies; probably not just combinations of two (or more) antihypertensive agents, but also the combination of various products which act on different cardiovascular risk factors. The need for such products is highlighted by the typical drug requirements of a diabetic patient who has suffered a myocardial infarction. The minimum drug requirements for such a patient include aspirin, statin, one (or more) oral hypoglycaemic agent, a beta blocker, an angiotensin-converting enzyme (ACE) inhibitor, and a fish oil preparation. Such a patient may also need further BP-lowering agents, a fibrate, and insulin.

However, given the need in most patients for at least

Table 1. Hypertension: unanswered questions

- Optimal first line agent
  - in subgroups (especially diabetes mellitus)
- Optimal drug combinations
  - in subgroups
- Optimal thresholds and targets
  - in subgroups
- Optimal concomitant medication (e.g. antioxidants, statins, aspirin)
  - in subgroups
- Impact on other end points
  - congestive heart failure and dementia

Table 2. 1999 WHO-ISH guidelines on future research

- BP and CVD in developing countries
- Alternative BP measurement
- BP lowering in high-risk patients
- More versus less BP lowering
- Evaluation of surrogate end points
- Combined interventions for CVD prevention
- Effects of newer BP-lowering agents
- Genetically targeted BP-lowering therapy

Key: WHO = World Health Organisation; ISH = International Society of Hypertension; BP = blood pressure; CVD = cardiovascular disease

two agents to control BP effectively, more trials of pairs of antihypertensive agents are required; ideally they are required in the setting of different patient subgroups (e.g. those with left ventricular hypertrophy, diabetes etc). Unfortunately, with one or two exceptions,[6] no trials are currently addressing this question. Hence, this area of enquiry should be a focus of hypertension trial activity during the next decade. Meanwhile, the British Hypertension Society (BHS) have recommended the AB/CD rule as a logical approach to combining drug classes.[7]

At what threshold should BP therapy be initiated?

Benefits of treating low-risk patients with a systolic BP in the range of 140–159 mmHg has not been validated in a randomised, placebo-controlled trial. It seems unlikely that any such trial will be carried out and yet the cost implication of treating BP in this range is massive. The trade-off of risk and benefit in this group should be evaluated in a trial. Meanwhile, most guidelines[4,8,9] recommend therapy at this threshold, which is totally impractical in most developing countries. Interestingly, guidelines (with the exception of JNC VII) increasingly recommend that thresholds for treating hypertension be based on estimated cardiovascular risk. It should be acknowledged, however that no trials have been designed to include patients on the basis of any such specific level of risk independent of BP. Hence, it is difficult and perhaps inappropriate, pending such information, to replace BP levels by risk levels when making treatment recommendations. It is likely that trials of patients with entry criteria based on estimated cardiovascular risk will be carried out during the next decade.

To what target should BP be lowered?

The shortcomings of the HOT trial[10] have been outlined previously[11] and highlight the need for a more definitive trial focused on systolic targets given the greater predictive value of systolic BP. The need for such a trial was included among the eight areas for further research included in the 1999 version of the World Health Organisation (WHO)-International Society of Hypertension (ISH) guidelines (table 2),[12] and should be carried out before the first decade of this century is over.

Tailoring therapy to patient subgroups: the developing world

Perhaps the most important glaring omission from among the eight areas of research recommended by WHO-ISH in 1999[12] is work in the developing world. This is the critical target for preventing the increase in the burden of hypertension and associated cardiovascular disease in the next two decades.[13] The potential for primordial prevention of raised BP and/or improved BP management remains in the developing world but only if suitable research is designed, resourced, and carried out urgently.

Optimising the implementation of guidelines

The most immediate challenge facing those who manage raised BP is to improve the rates of detection, treatment and control such that the current rule of two thirds[14] is drastically improved. This will come about by improved education and incentivisation of both the general population and the medical profession. The data shown in table 3 are a startling reminder that the vast majority of adults aged 60 years and above have levels of BP which currently 'merit' BP-lowering treatment. Whilst there is a real need for more effective drug therapies to improve the control of risk factors such as raised BP or cholesterol, it cannot be right to accept, as inevitable, the age-related increase in these classical risk factors and the mass medication and vast burden of disease which cardiovascular disease currently imposes. Only a population strategy to change diets and lifestyle from childhood onwards can avert the current situation and the anticipated global expansion of this problem.

Public education on health is achievable. At a population level, however, the advice given to the general public and

Table 3. Prevalence of hypertension*

Age range (years)	Men	Women
16–19	10.6	3.1
20–29	20.3	6.1
30–39	22.6	8.7
40–49	33.4	21.5
50–59	52.3	40.8
60–69	69.4	65.8
70–79	77.6	82.7
80+	81.8	83.8

Key: * Systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg

those responsible for healthcare delivery needs to improve dramatically. Despite some cynical views regarding large population-based interventions, startling beneficial effects on cardiovascular disease and mortality have been demonstrated at the population level. In Finland, for example, the reduction in cardiovascular deaths over a 20-year period, following a broad-based national campaign to improve diet and lifestyles, appears to have been almost completely attributable to the healthy life changes that were made.[15]

The improved implementation of guidelines necessitates more effective communication between those producing the guidelines and the healthcare professionals charged with managing patients. It is also likely to be useful to produce documents written, visual, or electronic, designed to inform the general public. Key features of ideal guidelines include simplicity, whilst being comprehensive, user friendly, easily interpreted and motivational. In the interests of optimal broad-based uptake of guidelines, simplicity is a pivotal component. Brief, simple messages with the inevitable trade-off of a degree of inaccuracy are required. For example, it has been suggested that drug intervention be based on a systolic BP threshold of 150 mmHg.[16] Levels above this should be treated and the target should be below 150 mmHg. Not much is lost by ignoring diastolic BP, except among younger patients (e.g. < 50 years) and whilst perhaps conservative, achieving this level of 'control' in the vast majority of those with hypertension would constitute a major improvement in BP management in countries such as the UK.[14] In the context of developing countries with restricted resources, such a policy may well have major advantages over trying to implement more aggressive guidelines produced out of context.[12]

Meanwhile physicians are duty-bound to at least inform the patients of benefits likely to arise from the prudent and appropriate use of currently-available agents shown in randomised trials to greatly reduce the risk of cardiovascular events.

References

1. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. *Lancet* 2000;**356**:1955-64.
2. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative 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.
3. McInnes GT. Commentary. ALLHAT: a saga of missed opportunities. *J Human Hypertens* 2003;**17**:373-7.
4. The JNC7 Report. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *JAMA* 2003;**289**:2560-72.
5. Wing LMH, Reid CM, Ryan P *et al.* for the Second Australian National Blood Pressure Study Group. 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. The ASCOT Steering Committee: Sever PS, Dahlof B, Poulter NR *et al*. Anglo-Scandinavian Cardiac Outcomes Trial: a brief history, rationale, and outline protocol. *J Human Hypertens* 2001;**15**:S11-S12.
7. Brown MJ, Cruickshank JK, Dominiczak AF *et al*. Better blood pressure control: how to combine drugs. *J Human Hypertens* 2003;**17**:81-6.
8. Guidelines Committee. 2003 European Society of Hypertension – European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003;**21**:1011-53.
9. WHO-ISH Writing Group. 2003 WHO/ISH statement on management of hypertension. (In press 2003).
10. Hansson L, Zanchetti A, Carruthers SG *et al*. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998;**351**:1755-62.
11. Sever P, Poulter NR. Hypertension trials – the current evidence base and forthcoming trials. *Br J Cardiol* 2002;**10**:640-4.
12. Guidelines Sub-Committee. 1999 World Health Organization – International Society of Hypertension guidelines for the management of hypertension. *J Hypertens* 1999;**17**:151-83.
13. Ezzati M, Lopez D, Rodgers A, Vander Hoom S, Murray CJ. Selected major risk factors and global and regional burden of disease. *Lancet* 2002;**360**:1347-60.
14. Primatesta P, Brookes M, Poulter NR. Improved hypertension management and control. Results from the Health Survey for England 1998. *Hypertension* 2001;**38**:827-32.
15. Vartiainen E, Puska P, Pekkanen J, Tuomilehto J, Jousilahti, P. Changes in risk factors explain changes in mortality from ischaemic heart disease in Finland. *BMJ* 1994;**309**:23-7.
16. Sever P. Simple blood pressure guidelines for primary health care. *J Human Hypertens* 1999;**13**:725-7.

Neil R Poulter
President, British Hypertension Society, and Professor of Preventive Cardiovascular Medicine
Imperial College London, Cardiovascular Studies Unit, NHLI, Faculty of Medicine, St Mary's Campus, London, W2 1PG.
(email: n.poulter@imperial.ac.uk)

Br J Cardiol 2003;**10**:418–20