Hypertension guidelines in the UK: a time for change

Bryan Williams

Hypertension is very common and is easily detectable. It is estimated that up to 40% of adults have raised blood pressure (BP) and, clearly, the proportion increases with age. The World Health Organization (WHO) identified high BP as the most important preventable cause of premature morbidity and mortality world-wide, ahead of smoking and elevated cholesterol.[1] Consequently, the treatment of hypertension plays a key role in the prevention of premature cardiovascular disease (CVD), which includes stroke. CVD accounts for about a third of all deaths in the UK.

The detection and treatment of hypertension make up a major outcome measure within the 'quality outcomes framework' for general practitioners in England. In 2001, it is estimated that the NHS funded 90 million prescriptions for drugs that lower BP, at a cost of £840 million: this represents nearly 15% of the total annual cost of all primary care drugs.

Hypertension is easy to detect. Importantly, its detection highlights the possibility that the patient may be at risk of CVD, not only by virtue of the BP, but also due to the common aggregation of other risk factors which serve to elevate the patient's CVD risk further. Thus, the measurement of BP is a simple screen for CVD risk, and a gateway to risk factor management.

What was the remit of the recent hypertension guideline update issued by NICE, working in collaboration with the British Hypertension Society (BHS)?

The original National Institute for Health and Clinical Excellence (NICE) hypertension guideline was issued in 2004 and its remit was 'the management of hypertension in adults in primary care'.[2] (This remit was not determined by NICE or by the guideline developers.) The remit specified that the guideline should cover advice about the detection, routine investigation, treatment and follow-up of uncomplicated hypertension in primary care. This includes advice on frequency of BP measurement, thresholds for intervention, BP treatment targets and the use of CVD risk assessment to guide treatment decisions in people with stage 1 hypertension.

The 2004 NICE guidance did not include advice on the treatment of hypertension in people with concomitant diseases such as diabetes, renal disease, stroke or heart disease. These are, or will be, covered by separate guidance focusing on these areas. Moreover, the remit did not include the provision of guidance for use of concomitant medications such as aspirin or statins to reduce CVD risk. The latter omission is unfortunate because GPs would like a single document on how to treat the patient to optimally reduce the risk, not just the BP, along the lines of the recent Joint British Societies' (JBS2) document.[3] The recently issued NICE/BHS updated guidance for the treatment of hypertension focuses on one section of the 2004 NICE guidance, namely 'the pharmacological treatment of hypertension'.

How did this rapid update of the NICE guidance come about and why was it necessary?

NICE guidelines are scheduled for routine review every five years to ensure that they remain current and that any new evidence is appraised. The decision to initiate a rapid update of national treatment guidance is not taken lightly. The main driver for this review was concern expressed about the efficiency of beta blocker-based treatment at reducing cardiovascular events, especially stroke, when compared to alternative treatment options.[4] The allied concern that beta blocker-based treatment, especially in combination with thiazide diuretics, enhances the risk of developing diabetes, when compared to other treatment options or the combination of

thiazide diuretics with drugs other than beta blockers, was also a consideration.[5] These concerns had emerged in recently published meta-analyses and were consolidated by the findings of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT).[6] It is clearly important that guideline development can work in 'response mode' and generate rapid guideline reviews and updates if and when necessary.

In mid-2005, NICE convened a multidisciplinary hypertension expert advisory group with representation of a number of national stakeholder organisations, which I was asked to chair. The group's remit was to advise the NICE executive whether a review of the existing NICE hypertension guideline was necessary. NICE accepted the recommendation of the expert advisory group that a review of the existing NICE guidance was warranted, specifically a revision of section 1.4 of the NICE hypertension guidance, which focused on the pharmacological treatment of hypertension. NICE then commissioned the National Collaborating Centre for Chronic Conditions (NCC-CC) to carry out this review and guideline update. A guideline development group (GDG) was convened which, working in collaboration with the BHS, undertook the rapid update of the guideline.

Why did NICE decide to work jointly with the BHS on this update?

Over the past 20 years, the BHS has produced a series of comprehensive and well regarded guidelines for the treatment of hypertension. The most recent, BHS IV, which was published in 2004,[7] coincided with the release of the first NICE hypertension guideline. It is important to emphasise that the BHS guidance had a less restrictive remit than the NICE guideline and discussed treatment in people with co-morbid diseases such as diabetes, renal disease and stroke. BHS IV also provided guidance on the use of concomitant medications, i.e. statins and aspirin, to reduce CVD risk optimally in people with hypertension.

The principal difference in treatment recommendations between BHS IV and NICE 2004 guidelines was the treatment algorithm. The BHS had recommended the use of the AB/CD algorithm which did not restrict initial therapy to a specific class of drug and recognised the fact that the magnitude of BP reduction with specific therapies may differ between younger people and older people. NICE 2004 generated an algorithm which recommended a thiazide-type diuretic as initial therapy for most people and did not differentiate treatment options based on age. Whatever the merits of either approach, two algorithms were in circulation and this was an undesirable state of affairs. The debate about which algorithm was the more appropriate or effective distracted from the real objective, which was to improve treatment. Moreover, neither guideline had the benefit of a formal cost-effectiveness analysis, which would have helped to consolidate their recommendations.

When it became clear that an update of the guideline was to be undertaken, it was logical that the opportunity should be grasped to revisit the treatment algorithm and to generate a single national treatment algorithm for hypertension. NICE and the BHS agreed a working relationship to develop the new guideline within the NICE guideline development framework. NICE worked with a number of stakeholders in addition to the BHS in the review of its guideline. These included the Blood Pressure Association (the patients' association for people with hypertension), the Primary Care Cardiovascular Society, the Nurses Hypertension Association and other patient/carer groups. The collaboration with the BHS was particularly significant, however, since the BHS agreed that the revised guideline would serve as an update to its own guideline to the pharmacological aspects of managing hypertension.

How was the guideline developed?

NICE commissioned the National Collaborating Centre for Chronic Conditions (NCC-CC) to undertake the rapid update of the guideline, working in collaboration with the BHS. A guideline development group (GDG) was convened and comprehensive systematic review of all treatment trials of BP-lowering therapy was undertaken, focusing primarily on head-to-head comparisons between different treatment strategies. It should be emphasised that the hypertension database is one of the largest in clinical medicine.[8] The principal efficacy outcomes analysed were myocardial infarction (fatal and non-fatal), stroke (fatal and non-fatal) and all-cause mortality. The development of diabetes or heart failure was also analysed for the cost-effectiveness analysis.

After the GDG reached its conclusions using data from the efficacy analysis, the data from the cost-effectiveness analysis were reviewed to determine whether they supported those from the efficacy analysis. The GDG then generated its draft recommendations, which were circulated to registered stakeholders, including the BHS guideline committee. The comments from the stakeholders are an essential and important part of the guideline development process. The stakeholder comments were reviewed by the GDG and further analyses undertaken before the final draft recommendations were produced. Thereafter followed a series of detailed editorial meetings with NICE, culminating in the production of the final guideline, a quick reference guide, an 'information for the public' leaflet and a detailed assessment of the economic impact of implementing the guideline recommendations.

This was an extraordinarily rigorous and professional process and it is clear that this methodology is the template for modern guideline development.

Key messages in the NICE/BHS hypertension guideline update:

The NICE/BHS guideline has four key changes: i) a new national algorithm to guide drug selection for treatment of hypertension; ii) recognition that ethnic group and age can influence initial drug selection; iii) the downgrading of beta blockers as a routine initial therapy for hypertension; iv) the incorporation of a formal cost-effectiveness analysis to underpin the recommendations.[9,10]

The treatment algorithm

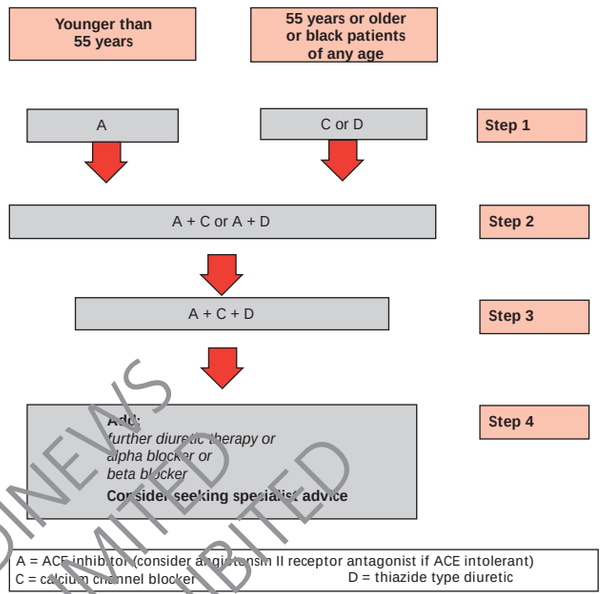
The guideline contains a simple treatment algorithm for initiating drug therapy for hypertension (figure 1) and for logical drug combinations for patients who require more than one drug to control their BP. The efficacy analysis revealed that calcium channel blockers (C) or thiazide-type diuretics (D) were the most effective initial therapy for hypertension. This reflects the fact that almost all clinical outcomes data have been obtained in patients over the age of 55 years, in whom C or D are likely to be the most effective at lowering BP. For younger patients, i.e. those below the age of 55, there are fewer data to guide clinical practice.[11,12] One option would have been to apply the data to all ages but this would not have been appropriate, especially when one considers data suggesting that angiotensin-converting enzyme (ACE)-inhibitors or angiotensin II receptor blockers (ARBs) (A) may be more effective than C or D at lowering BP in younger people. In the absence of clinical outcome data for younger people, the GDG used blood pressure-lowering efficacy to determine the choice of treatment in younger people and recommended initiating therapy with A (an ACE inhibitor or an ARB if ACE inhibitors are not tolerated).

Many patients require more than one drug to control their BP and the recommendation for step 2 is to combine A + D or A + C. For those requiring three drugs, A + C + D is recommended. These are logical combinations, frequently used in clinical practice and commonly used in the clinical trials that have formed the evidence base for treating hypertension. For patients whose BP is not controlled on three drugs, further diuretic therapy is recommended. Options to consider include higher doses of thiazide-type diuretic, spironolactone or amiloride. However, more intensive monitoring of electrolytes and renal function will be required when using such combinations. For a patient with BP uncontrolled by three drugs, a longer acting alpha-blocker or a beta blocker provides an alternative option. In patients who are resistant to three drugs, specialist advice should also be considered.

Recognition that ethnic group and age can influence initial drug selection

The guideline recommends that C or D would be the preferred initial therapy for the treatment of hypertension in people of Black African origin, at all ages. This is supported by the data from the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT), which showed that C or D were more effective at initial BP lowering when compared to A in people over the age of 55 years and especially in Blacks.[13,14] The influence of age has been discussed above.

Figure 1. Choosing drugs for patients newly diagnosed with hypertension



Black patients are those of African or Caribbean descent and not mixed race, Asian or Chinese patients

Beta blockers

- Beta blockers are no longer preferred as a routine initial therapy for hypertension
- But consider them for younger people, particularly:
  - women of childbearing potential
  - patients with evidence of increased sympathetic drive
  - patients with intolerance of or contraindications to ACE inhibitors and angiotensin II receptor antagonists
- If a patient taking a beta blocker needs a second drug, add a calcium-channel blocker rather than a thiazide-type diuretic, to reduce the patient's risk of developing diabetes
- If a patient's blood pressure is not controlled by a regimen that includes a beta blocker (that is, it is still above 140/90 mmHg), change their treatment by following the flow chart above
- If a patient's blood pressure is well controlled (that is, 140/90 mmHg or less) by a regimen that includes a beta blocker, consider long-term management at their routine review. There is no absolute need to replace the beta blocker in this case
- When withdrawing a beta blocker, step down the dose gradually
- Beta blockers should not usually be withdrawn if a patient has a compelling indication for being treated with one, such as symptomatic angina or a previous myocardial infarction

The downgrading of beta blockers as a routine initial therapy for hypertension

This decision has received the most attention but was actually the easiest decision to make on the basis of the analysis of evidence. Put simply, beta blocker-based therapy was: a) the least effective treatment at preventing major cardiovascular events, especially stroke; b) more likely to increase the risk of developing diabetes (especially when combined with a thiazide); and c) was dominated in the cost-effectiveness analysis by all other treatment options, and was the least cost-effective treatment option.[9]

This does not mean that beta blocker-based therapy is ineffective. Clearly, any drug therapy that lowers BP is likely to be effective at reducing cardiovascular events over the longer term and the clinical trial evidence supports that view. However, beta blocker-based therapy was less effective than alternative treatments, especially at preventing stroke. There are patients who will require the benefits of beta blocker-based therapy beyond their impact on BP, notably those with angina, post-myocardial infarction and in chronic stable heart failure, and the guideline recommends that they should continue with this medication. Beta blocker-based therapy is also a treatment option for patients who have tried other drugs but cannot tolerate them, or for those who require additional drug therapy for resistant hypertension, or for women of childbearing potential in whom the A drugs will not be used. Thus, whilst beta blocker-based therapy will undoubtedly decline as a routine treatment for hypertension, there are still some patients for whom beta blockers will be a preferred treatment choice.

Finally, concern has been expressed as to whether the caution about beta blockers should apply only to atenolol (which has been the main drug in the class which has been tested in the hypertension trials) and should not be extended to all beta blockers – which have not been tested in hypertension trials. Whilst there are theoretical reasons why other beta blockers with different pharmacological properties might be more effective than atenolol in people with hypertension, it would not be appropriate to recommend their use on the basis of 'they might have done better!' in the absence of any clinical outcome trials in hypertensive patients.

The incorporation of a formal cost-effectiveness analysis to underpin the recommendations

In addition to examining the efficacy of drugs at preventing major cardiovascular events and premature death, it is also important to gain insights into the balance between costs of treatment (drug costs and cost of any associated adverse effects) and effectiveness in terms of cost savings from preventing events. This approach is based on the use of Markov modelling, which requires calculation of a number of transition probabilities from various health or disease states to clinical events, and the favourable or unfavourable impact of different types of treatment on these transition probabilities. These analyses are sensitive to a number of assumptions, including the baseline risk of an individual patient transiting to various health states. These analyses do not drive the recommendations but are important because they define whether a specific intervention is cost-effective in the context of treatment choices for hypertension and relative to other healthcare interventions. With regard to the former, the cost-effectiveness analysis supported the initial drug treatment choices in the treatment algorithm and showed beta blockers to be the least cost-effective treatment option. With regard to the latter, the treatment of hypertension was revealed to be extraordinarily cost-effective, at less than £1,000 per QUALY.[9]

The cost impact of the guideline was also estimated. If the recommendations were fully implemented, the annual recurrent cost impact for England would be around £58 million in additional drug costs. However, the purpose of changing the recommendations was to ensure that patients receive the most effective treatments and thus to improve clinical outcomes. It is estimated that full implementation of the guideline would result in significant savings through a reduction in the number of clinical events, especially strokes. Since this saving is estimated as being £280 million, an overall net saving arising from implementation is estimated, at £222 million. This is likely to be an underestimate of the benefits because the greater use of more rational drug combinations will result in improved BP control and even better clinical outcomes.

What will be the impact of this guideline?

This guideline will have significant impact. The strong endorsement of the guideline by professional societies and the generation of a single pragmatic algorithm to guide treatment will aid implementation. This, allied to other changes in the UK, notably the National Service Frameworks and the incentivised Quality Outcomes Framework, will undoubtedly lead to improvements in detection, treatment and control rates for BP in the UK.

Beyond the UK, there is little doubt in my view that the rigour of this guideline development process, led by a national organisation (NICE) but engaged with the relevant specialist society (the BHS) and embracing a wide range of stakeholders, is the only way forward for the development of modern treatment guidelines. Other professional societies engaged in guideline development world-wide should take note.

Potential conflict of interest

BW is past-President, British Hypertension Society; Chairman BHS guidelines working party; Clinical Advisor to the NICE hypertension guideline development group 2005/6.

References

1. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: Analysis of world-wide data. *Lancet* 2005;**365**:217-23.
2. National Institute for Clinical Excellence (NICE) Clinical Guideline 18 –– Management of hypertension in adults in primary care. 2004 www.nice.org.uk/CG018NICEguideline
3. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. British Cardiac Society, British Hypertension Society, Diabetes UK, HEART UK, Primary Care Cardiovascular Society, The Stroke Association. *Heart* 2005;**91**(suppl V):V1-V52.
4. Lindholm LH, Carlberg B, Samuelsson O. Should β-blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet* 2005;**366**:1545-53.
5. Mason JM, Dickinson HO, Nicolson DJ, Campbell F, Ford GA, Williams B. The diabetogenic potential of thiazide-type diuretic and beta-blocker combinations in patients with hypertension. *J Hypertens* 2005;**3**:1777-81.
6. Dahlöf B, Sever PS, Poulter NR *et al.,* for the ASCOT investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005;**366**:895-906.
7. Williams B, Poulter NR, Brown MJ *et al.* Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV. *J Hum Hypertens* 2004;**18**:139-85.
8. Williams B. Recent hypertension trials: implications and controversies. *J Am Coll Cardiol* 2005;**45**:813-27.
9. NICE/BHS. Clinical guideline 34: hypertension: management of hypertension in adults in primary care: partial update. http://www.nice.org.uk/CG034guidance (accessed June 28, 2006).
10. Williams B. Evolution of hypertensive disease: A revolution in guidelines. *Lancet* 2006;**368**:6-8.
11. Dickerson JE, Hingorani AD *et al.* Optimisation of antihypertensive treatment by crossover rotation of four major classes. *Lancet* 1999;**353**:2008-13.
12. Deary AJ, Schumann AL, Murfet H *et al.* Double-blind, placebo-controlled crossover comparison of five classes of antihypertensive drugs. *J Hypertens* 2002;**20**:771-7.
13. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. *JAMA Express* 2002;**288**:2981-97.
14. Wright JT Jr, Dunn JK, Cutler JA *et al.,* for the ALLHAT Collaborative Research Group. Outcomes in hypertensive black and nonblack patients treated with chlorthalidone, amlodipine, and lisinopril. *JAMA* 2005;**293**:1595-608.

Professor Bryan Williams
Professor of Medicine,
University of Leicester School of Medicine,
Clinical Sciences Building,
PO Box 65, Leicester Royal Infirmary,
Leicester, LE2 7LX.
Correspondence to: Professor B Williams
(email: bw17@le.ac.uk)

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Diary

2006

2nd-6th September: World Congress of Cardiology. A joint meeting of the European Society of Cardiology and the World Heart Federation, Barcelona, Spain.
Contact: World Heart Federation, Switzerland; tel: +41 22 807 03 20; fax: +41 22 807 03 37;
email: congress@worldheart.org

22nd-23rd September: ARTERY 6, Athens, Greece.
Contact: Hampton Medical Conferences Ltd; tel: 020 8783 2230; fax: 020 8979 6700;
email: zcorbett@hamptonmedical.com; website: www.hamptonmedical.com

5th-7th October: Primary Care Cardiovascular Society Annual Scientific Meeting, Newcastle Gateshead, UK.
Contact: PCCS: Tel: 020 8994 8775; fax: 020 8742 2130; email: office@pccs.org.uk

13th October: Women's Heart Alliance Symposium, '2nd Fashioning a New Approach to Coronary Care in Women', Royal College of Physicians, London.
Website: www.womensheartalliance.com

12th-15th November: American Heart Association Annual Meeting, Chicago, Illinois, USA.
Website: www.scientificsessions.org

17th-18th November: 4th Annual British Junior Cardiologists' Association, Manchester.
Contact: LeapFrog Medical (meeting secretariat); tel: 01293 827164; email: bjca@leapfrogmedical.com

20th November: Cardiac Disease and Pregnancy, Royal College of Obstetricians and Gynaecologists, London.
Fax: 020 7772 6388; website: www.rcog.org.uk/meetings

23rd-24th November: Scottish Heart and Arterial Risk Prevention (SHARP) Winter Scientific Meeting, Perthshire, Scotland.
Contact: Dr SR McEwan; Tel: 01382 660111, ext 33124; email: s.r.mcewen@dundee.ac.uk