Hypertension in practice: towards the year 2010

This review is based on the premise that the majority of hypertensive patients are managed by primary healthcare teams comprising both doctors and specialist nurses. It attempts to provide clinical guidance, taking into account the large number of important long-term outcome studies published since the millennium. It is now clear that clinical decisions should be made on the basis of the systolic rather than diastolic blood pressure. It is also now increasingly evident that blood pressure readings taken at home are more predictive of outcome than isolated raised readings taken in the clinic. Patients should now be encouraged to obtain their own blood pressure machine in order to provide reliable readings in a familiar nonstressed setting. The threshold for starting antihypertensive medication depends on the patients' total cardiovascular risk, rather that just the height of the blood pressure. In particular, blood pressure should be managed aggressively in patients who have concurrent diabetes mellitus. There is now good evidence that such treatment is of value in all ages, including patients over the age of 80 years. There has been radical change in the choice of first-, second- and third-line drugs, with a steady decline in the use of β-blockers and an increase in the popularity of the angiotensin-blocking drugs. These agents are now the first-line choice in younger patients, those with diabetes and/or chronic renal impairment. The long-term outlook for a patient is more closely related to the quality of blood pressure control at follow-up, rather than the severity of the hypertension in the first place. Well-organized clinical care, with an increasing involvement of nurses, can achieve the required targets.

KEYWORDS: assessment, hypertension, practice, risk, treatment

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Since the millennium, there have been a great many clinical and therapeutic studies, which have radically altered our view of the management of hypertension. Several long-term outcome trials have been published comparing different drug classes in the prevention of cardiovascular disease (CVD) [1–6]. We have also seen the launch of aliskiren, the first of a new class of antihypertensive agents [7].

In 2008, the Hypertension in the Very Elderly Trial (HYVET) was published [8]. This is an historic event, as it is probably the last long-term outcome trial to compare active therapy with placebo tablets. Such trials will, from now on, be unethical, as withholding active treatment means that patients with hypertension are denied the proven benefits of blood pressure reduction.

In 2006, the British Hypertension Society (BHS) and the UK National Institute of Health and Clinical Excellence (NICE) stepped out of line with other guideline providers in Europe and the USA with radically new ideas on its optimum choice of first-, second- and third-line antihypertensive therapy [9]. There is therefore a lot to discuss.

This review seeks to interpret the new information and provide suggestions for the optimum method of controlling blood pressure. The review is written with the premise that the majority of patients are managed exclusively in primary care, with only a few requiring referral to specialist centres. Clinicians in secondary care centres may find this approach to be too simplistic. However, the management of the world's most common chronic disease requires a simple and feasible approach for millions of people. Worldwide, hypertension is associated with 7.6 million premature deaths, 54% of all strokes and 47% of heart attacks [10]. Only through efficient primary care and action to improve public health can these alarming statistics be reversed.

Blood pressure & risk

The relationship between the height of the systolic and diastolic blood pressure and the risk of heart attack and stroke is continuous, extending down to pressures that are below the population average [11]. There is no discernable threshold between hypertension and normotension. An individual with a systolic blood

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pressure of 130 mmHg has a greater CVD risk than a similar person with a systolic pressure of 115 mmHg. From a clinical point of view, however, hypertension is best defined as that level of blood pressure above which investigation and treatment do more good than harm [12]. The level of blood pressure at which treatment should be instigated depends on an individual's risk of heart attack and stroke, as well as the currently available evidence of the benefits of treatment. Very-high-risk patients, such as those with Type 2 diabetes mellitus or renal disease, would have a lower threshold for treatment than younger low-risk patients.

However, the treatment of patients defined as hypertensive by the above criteria will not solve the problem of the high incidence of heart attacks and strokes in developed countries and the rising incidence in developing countries. An epidemiologist would also want to see a real fall in the population average blood pressure, albeit of modest proportions. This could have a major impact on the number of heart attacks and strokes in the population, including those people whose blood pressures are at or just below the population average. There is now evidence that population average blood pressures are falling, although the mechanisms for this are uncertain [13]. The trend might be related to a reduction in salt intake and an increase in the consumption of fruit and vegetables. This fall in average blood pressure has occurred despite an increase in the average weight of the population and an increasing prevalence of overweight and obesity.

In older people, the population average blood pressure and the prevalence of hypertension are rising. This is partly because more people with hypertension are receiving antihypertensive treatment, thus avoiding heart attacks and strokes. They are now living longer and swelling the ranks of the elderly hypertensive population.

There is increasing interest in people whose blood pressures are below the threshold for prescribing antihypertensive treatment, but who are at greater CVD risk than people with optimal blood pressure [14]. As blood pressure rises with age, and higher blood pressures rise faster than lower pressures, many of these people, in the fullness of time, do become clinically 'hypertensive', requiring treatment. These people are classified by some as 'pre-hypertension' or 'high normal'. Might blood pressure reduction in this pre-hypertensive stage, possibly on a short-term basis, delay the progression to clinical hypertension? Two trials have addressed this issue, but the results and their significance are uncertain. One trial suggested that on stopping treatment blood pressures rise slower than in those given no treatment. By contrast, another trial suggested that on stopping treatment, blood pressure simply rises to the pretreatment levels, so nothing has been achieved [15,16].

Systolic versus diastolic blood pressure

Up until the 1980s, students were taught that height of the diastolic blood pressure was more important or predictive than the systolic pressure. This 'conventional wisdom' was actually on the basis of no evidence. To answer the question on the relative importance of these two indices of pressure, it is necessary to obtain long-term follow-up data on large populations. One of the first major studies to suggest that systolic pressure overrides diastolic pressure was the Framingham Project, published in 1971 [17]. In addition to reliable data, it was also necessary to apply statistical tests that are able to differentiate the predictive power of systolic versus diastolic pressures, whilst taking into account other CVD risk factors including age, plasma lipid levels, concurrent diabetes mellitus and prior cardiovascular end-organ damage. The technique necessary was the Cox's proportional hazard model. In addition, it was also necessary to use computer hardware and software, which was not available until the 1990s. Since then, many follow-up studies, including the Framingham Project, have confirmed that over the age of about 40 years, the height of the systolic pressure did indeed have more predictive power than the diastolic pressure. Below this age, where numbers are small, there remains some uncertainty about the relative importance of the two measures of blood pressure, and it appears that diastolic may still be pre-eminent [18].

These population studies have also suggested that the pulse pressure (i.e., systolic pressure minus diastolic pressure) may be the best predictor of risk. In this respect, it is interesting that the two studies of the treatment of isolated systolic hypertension in the elderly (Systolic Hypertension in the Elderly Program [SHEP] and Systolic Hypertension in Europe [SYST-EUR]) both demonstrated that systolic blood pressure reduction was very worthwhile, even though the diastolic pressure was not raised [19,20]. There are no suggestions that pulse pressure should be a therapeutic target, but it is notable that when treating isolated systolic hypertension, the reduction in systolic blood pressure is numerically greater than the reduction in diastolic pressure, so pulse pressure is reduced.

These data have prompted authors to suggest that diastolic blood pressure should no longer be measured; all decisions being made on the basis of the systolic pressure [21,22]. This opinion may come as a surprise to many doctors and nurses who are still taught that diastolic pressure is more important. With the aging population and improved survival of younger hypertensives, the total number of people being defined as having hypertension is rising.

The size of the problem

Approximately 10 million people in the UK have hypertension of the level where treatment should be seriously considered [23]. Hypertension is now the most common chronic clinical condition in the developed and developing worlds, and the most prevalent risk factor for premature death. From a practical point of view, each general practitioner in the UK can expect to have between 200 and 250 hypertensive patients on their list [24]. It is the most common single long-term medical problem requiring treatment in primary care.

Detection

As most hypertensive patients are asymptomatic until late on in their disease progression, they can only be detected by systematic screening of apparently fit people. Hypertension is 'the silent killer', which will go undetected unless special efforts are made. This is best achieved within the context of primary care and in the UK, with the new General Medical Services (GMS) contract, better detection is being achieved. Approximately 80% of people visit their primary healthcare team or have some contact with a clinician at least once over a 3-year period, and this should be the obvious time to conduct 'opportunistic screening' [24]. It is very difficult to reach the remaining 20% who have no medical contact for years on end. Population surveys still show that somewhere between a quarter and half of all hypertensive patients have never had their blood pressure measured and many remain undiagnosed until the time of their heart attack or stroke. It is commonly reported that the rates of detection, treatment and control of blood pressure in the UK are inferior to that seen in other developed countries, although some of these international comparisons do not bear close examination. Data from the Health Survey for England strongly suggest that, with the recently introduced primary care targets for opportunistic screening, things are improving [23].

Assessment

It is now clear that a single casual 'one-off' blood pressure reading provides little useful information unless it is very high. It has recently been demonstrated that in a low-risk woman below age 35 years, the diagnosis of hypertension is more likely to be due to measurement error than to genuine hypertension [25]. Blood pressures frequently settle on retesting, and there is increasing evidence that clinic or 'office' blood pressure readings are less predictive than accurate home blood pressure recordings or 24-h ambulatory blood pressure monitoring (ABPM). In clinical practice, it appears that blood pressures tend to 'bottom out' at about the fourth consultation [26]. All too often, patients begin drug treatment on the basis of a single casual raised blood pressure reading. With careful clinical assessment, many of these patients can avoid or at least delay the need for antihypertensive drugs. These patients might be diagnosed as having 'white-coat' hypertension, implying that their pressures are only raised in the clinical setting. The long-term significance of white-coat hypertension is, however, a little uncertain. A recent meta-analysis of several long-term studies of patients with sustained hypertension, white-coat hypertension and those with no hypertension, strongly suggests that the outcome for white-coat hypertension is not different from those with normotension [27]. By contrast, studies of left-ventricular wall thickness and carotid intima-media thickness, including a follow up study, suggest that white-coat hypertensives have less vascular damage than sustained hypertensives, but more than normotensives [28,29].

One advantage of the declining use of mercury manometers is that, with accurate electronic equipment, the clinician can effortlessly take three or four readings at each consultation, overcoming some of the white-coat effect, as well as avoiding observer error. Of the four sources of error in blood pressure measurement (the clinician, the patient, the manometer and the cuff), observer error and bias are by far the most important [30] (Figure 1). The use of the mercury manometer and stethoscope (the Riva Rocci–Korotkoff technique) is rapidly declining due to the major problem of observer error, as well as concerns over the environmental toxicity of mercury [31].

Most hypertensive patients require little detailed investigation. However, routine urine dipstick testing is mandatory. The presence of proteinuria raises the possibility of an underlying renal cause for the high blood pressure.

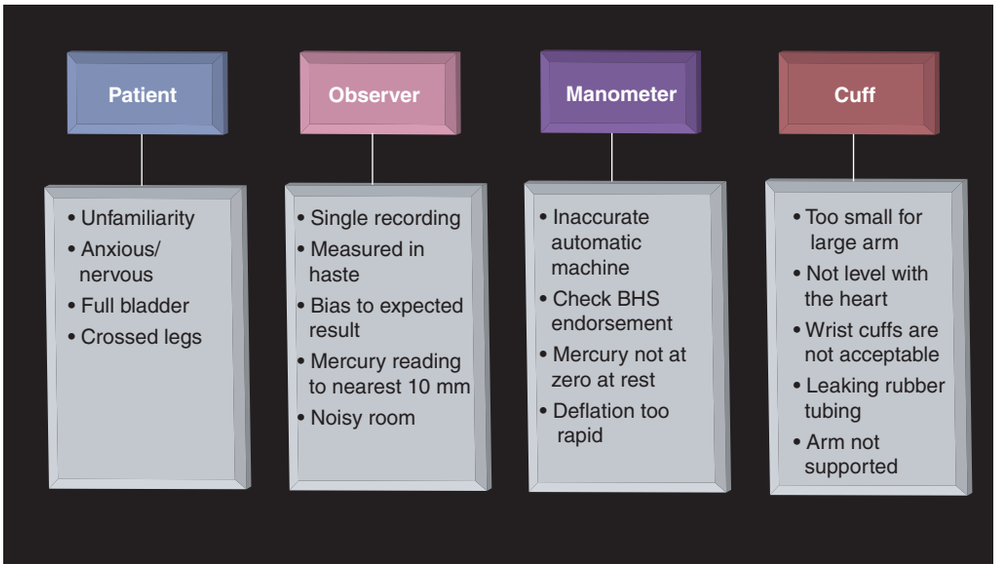

Figure 1. Sources of error in blood pressure measurement. The largest sources of error are those due to the observer. These can be minimized with the increasing use of semi-automatic monitors.
BHS: British Hypertension Society.

These patients with renal disease have a greatly increased cardiovascular risk, and are more likely to die of a heart attack or stroke than from their primary renal condition. Even if no intrinsic renal disease is detected, the presence of proteinuria in dipstick testing indicates an approximately two- to four-fold increase in cardiovascular risk [32,33]. All patients should also have a routine estimation of serum creatinine, urea, sodium and potassium levels. Measurement of plasma glucose, total and high-density lipoprotein cholesterol is also necessary to estimate the patient's total cardiovascular risk [34]. It is usually recommended that these tests are taken in the fasting state, but this can be inconvenient in afternoon clinics or evening consultations. In fact, fasting (i.e., missing a light breakfast) has only a 5–10% effect on blood glucose and cholesterol levels, an error that is within the coefficient of replicate variation within or between assays. A nonfasting cholesterol or glucose that is unequivocally normal is much better than no test at all.

There has recently been increased interest in the calculation of an estimated glomerular filtration rate (eGFR) on the basis of the patient's serum creatinine, age and gender. The eGFR is calculated from the four-variable version of the modification of diet and renal disease (MDRD) formulae [35]. This system has not been validated in the hypertension clinic or in general practice, and its value in the elderly must be seriously questioned [36,37].

If these baseline tests are all normal, no further action is required. If the tests are abnormal, and particularly if the serum potassium is below 3.6 mmol/l, whilst not receiving diuretic therapy, specialist referral is necessary to exclude the relatively rare (5%) underlying renal and adrenal causes of hypertension.

It is mandatory that hypertensive patients should have a 12-lead electrocardiogram (ECG). Within general practice, approximately half of all hypertensive patients will be found to have an abnormal ECG, and approximately 8% have evidence of left ventricular hypertrophy (LVH) [38]. Whilst the ECG is a relatively insensitive method for detecting LVH, it is reasonably specific (i.e., if the ECG shows LVH, then LVH will be confirmed by electrocardiography). The most commonly used criteria for the detection of LVH are the Sokolov and Lyon criteria [39]. The depth of the S-wave in lead V1 and the height of the R-wave in lead V5 or V6 (whichever is greater) should be below 35 mm in normal individuals. Values above this figure are suggestive of LVH. However, it is worthwhile remembering that the chest leads are unipolar, and therefore greatly influenced by the distance from the heart. Therefore, false-negatives can occur in patients who are very obese, and occasionally false-positives can occur in patients who are extremely slender. A less commonly used, but probably more reliable method of assessment of LVH on the ECG, is the Cornell voltage criteria. If the sum of the

R wave in lead aVL and the S-wave in lead V3 is more than 28 mm in men and 20 mm in women, then LVH is almost certainly present. If the blood pressure is raised but there is absolutely no LVH on the ECG, then the white-coat effect should be suspected. A 24-h ABPM may show that pressures are much lower or even normal when the patient is away from the clinic. If LVH is definitely present, then 24-h ABPM may be unnecessary as the cardiovascular prognosis is increased three- to four-fold. The risk is even higher if repolarization abnormalities in leads V4 to V6 (LV strain) are also present.

Nonpharmacological lowering of blood pressure

It has been calculated that a small but genuine reduction in the population average blood pressure could dramatically reduce the burden from CVD [40]. Lowering the diastolic blood pressure by only 2 mmHg in middle-aged people could reduce the prevalence of stroke by 15% and coronary heart disease by 6–9%. This amount of blood pressure lowering in the general population could be achieved by dietary and lifestyle interventions, applied at a public health level. There is evidence that population average blood pressures have fallen over the last 20 years, and this may partly explain why both heart attack and stroke incidence has fallen [13].

Several lifestyle modifications have been shown to be effective in the lowering of blood pressure. In normotensive people, a reduction in body weight of 5.5 kg leads to a reduction in systolic blood pressure of 4.4 mmHg, and diastolic blood pressure by 3.6 mmHg, and a 20% reduction in the development of new-onset hypertension [41].

Several meta-analyses have demonstrated the efficacy of dietary salt reduction in lowering blood pressure. The randomized Dietary Approaches to Stop Hypertension (DASH) low-sodium trial confirmed a progressive lowering of blood pressure with reductions in sodium intake [42]. Further reductions in blood pressure were observed with an increased consumption of fruit and vegetables and a reduction in dairy products.

Other interventions that have been shown to have a beneficial effect on blood pressure lowering include increased aerobic exercise, potassium supplementation and a reduction in alcohol intake. The benefit of fish oils and herbal supplements remains uncertain.

In practice, it is extremely difficult to make these dietary modifications. In Western societies, only approximately 10% of an individual's daily salt intake is explained by the addition of salt at cooking or at table [43]. The rest is already in foods, particularly ready meals, snacks, cereals and bread. Widespread implementation of better labeling and regulation of the food industry is necessary to substantially lower the salt intake in the general population. Despite these difficulties, appropriate diet and lifestyle advice should be given to all hypertensive patients, and implementing these measures may reduce or even obviate the need for pharmacological therapy in some patients.

Drug treatment

The British guidelines recommend two thresholds for starting drug treatment. In low-risk individuals, they recommend starting treatment if the blood pressure is persistently greater than 160/100 mmHg (Figure 2). For high-risk individuals they recommend treatment above 140/90 mmHg [34]. A patient's cardiovascular risk status can easily be calculated using the color charts available from all these guidelines listed earlier. Current guidelines advocate the use of antihypertensive drugs if the patients cardiovascular risk status means there is a 20% chance of developing a heart attack or stroke in the next 10 years [44]. The target blood pressure recommended in the British guidelines is 140/85 mmHg, with the lower target of 140/80 mmHg in patients who also have diabetes mellitus.

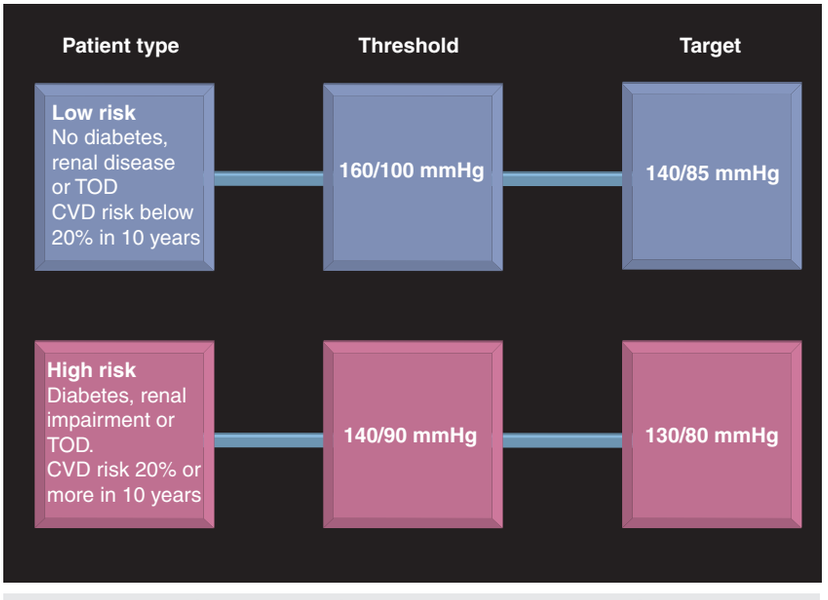

Figure 2. A simplified version of the thresholds and targets for the drug treatment of hypertension. These are the recommendations of the British Hypertension Society (BHS) in their 2006 guidelines, and those of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) in 2007. CVD: Cardiovascular disease; TOD: Target organ damage.

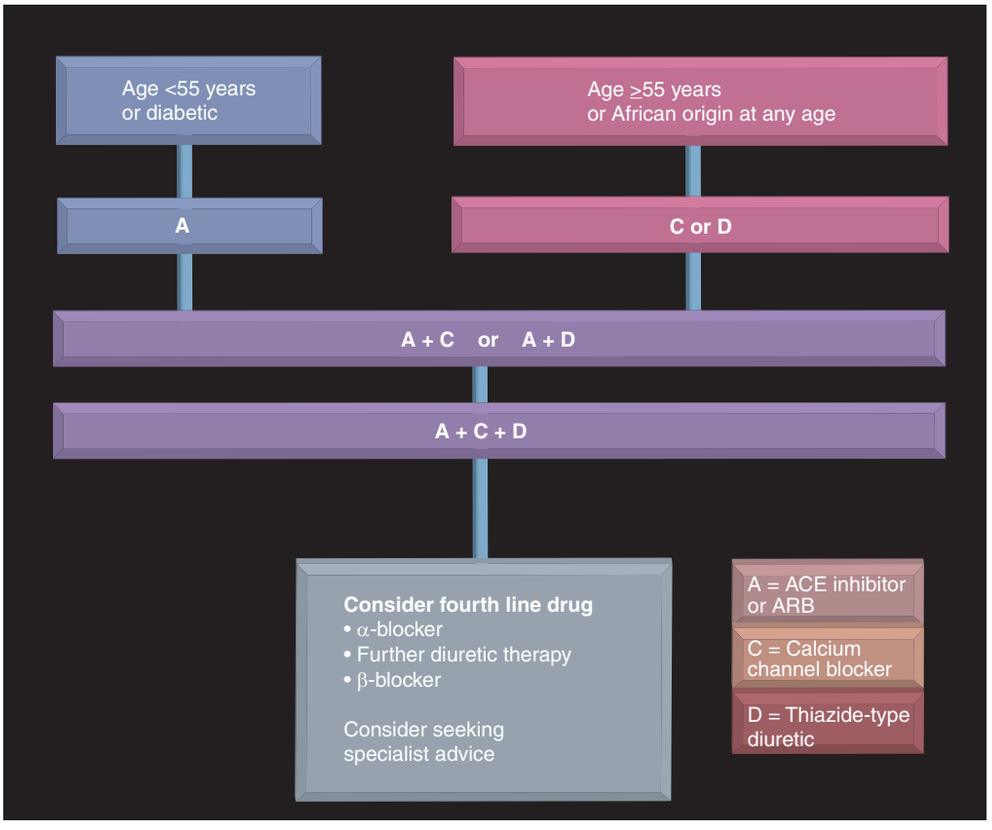

Figure 3. The sequence of choice for the first-, second- and third-line agents to control blood pressure. Note that the β-blockers should not be used unless there are specific indications, but they can be considered as fourth-line agents.
ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker.

The threshold for starting antihypertensive drug therapy is based on a large number of extremely well-conducted trials. These demonstrate that lowering blood pressure reduces strokes by approximately 40%, and heart attacks by 20% [45]. In 2007, a placebo-controlled trial in patients over the age of 80 years (HYVET) was terminated with evidence that even at this age, blood pressure lowering is worthwhile, with prevention of strokes, heart failure and all-cause mortality [4].

If the decision is made to not treat patients with borderline hypertension, it is important that they have very careful follow-up and the decision to withhold treatment should be revisited regularly. Careful clinical assessment with measurement of total CVD risk is essential.

A choice of first-, second- & third-line antihypertensive drugs

If antihypertensive drug treatment is required, it is important that appropriate therapy is chosen. For many years, β-blockers were considered to be the optimum first-line therapy. This was partly due to the view that there was strong evidence supporting the use of β-blockers in the secondary prevention of coronary heart disease in heart attack survivors. Therefore, it was argued that the β-blockers may also be beneficial in the primary prevention of CVD in hypertensive patients. Analysis of the available long-term outcome trials in uncomplicated hypertension did not, however, provide any evidence that β-blockers were superior to other agents at preventing heart attacks. In the Losartan Intervention for Endpoint (LIFE) trial of atenolol versus losartan and the Anglo Scandinavian Cardiac Outcomes Trial (ASCOT-BPLA) of an atenolol-based regime versus an amlodipine-based regime, atenolol proved to be inferior to the comparator drugs at stroke prevention, and was associated with more new-onset Type 2 diabetes mellitus [1,2]. In a subsequent meta-analysis of other trials that also used atenolol, it was concluded that this agent is not suitable for the first-line treatment of hypertension [46]. A later meta-analysis, from the same group, which included all β-blocker trials, came to the same conclusion [47]. These findings led the BHS and NICE to remove β-blockers from their ABCD system of treating

hypertension, which thus became the ACD system [48] (FIGURE 3). This radical turnaround in response to new information has not yet been reflected in the guidelines provided by the US Joint National Committee or the International or European Societies of Hypertension.

β-blockers do still have an important role in some patients with hypertension, and are almost mandatory in those with angina pectoris and those who have had a heart attack, have heart failure or some tachyarrythmias. They remain useful in patients with migraine and those who are over-anxious. Clinicians should only use β-blockers if there is a specific indication, but otherwise not in the 'routine' clinical care of hypertension [49].

The choice of first-line drugs is related to the renin status of the patient [50]. There is reliable evidence that drugs that block the renin–angiotensin–aldosterone system (the angiotensin-converting enzyme inhibitors [ACE-Is], the angiotensin receptor blockers [ARBs], the β-blockers and, more recently, the direct renin inhibitors) are less effective in patients whose plasma renin levels are low. As plasma renin falls steadily by approximately 50% between the age of 20 and 60 years, these drugs are less effective in the elderly. Furthermore, plasma renin levels in African-origin patients are approximately half of those seen in other ethnic groups. It follows that ACE-Is and ARBs are less effective in African-origin patients. Patients with Type 2 diabetes also have low plasma renin levels [51]. However, in these patients, although the blood pressure-lowering effects of the ACE-Is and ARBs is modest, these drugs should be used early in the treatment of hypertension, as they appear to be effective in delaying progression of diabetic nephropathy, probably due to a direct effect on the postglomerular efferent arterioles, thus reducing intraglomerular pressure [52]. However, the modest effect on blood pressure means that second- and third-line drugs are almost always necessary.

It is not current practice to measure plasma renin levels in hypertensive patients. This would not be cost-effective, and there are technical difficulties in doing this in general practice, as samples need to be sent to the laboratory immediately for analysis. Furthermore, many antihypertensive drugs affect plasma renin levels that are also dependent on the patients' salt intake. It is therefore simply better to base the choice of antihypertensive treatment on the patient's age and ethnicity [53].

In older patients and those of African origin, the guidelines recommend that the first-line

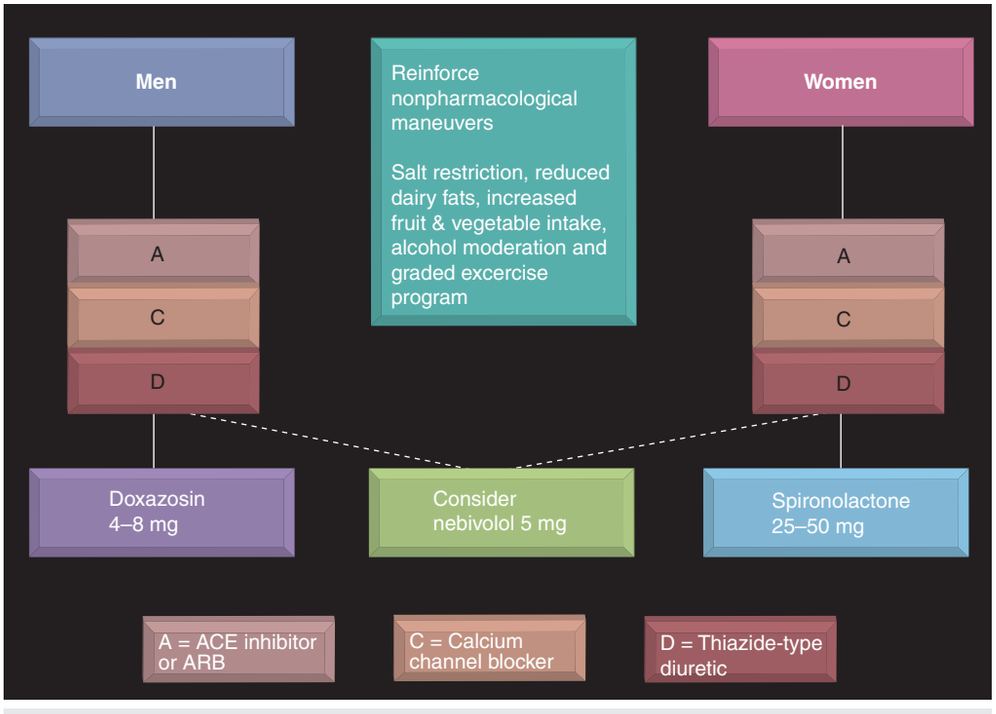

Figure 4. The current management of hypertension used in the Blood Pressure Clinic at the City Hospital, Birmingham, UK. Note that none of the recommendations for fourth-line drug therapy are based on randomized controlled trials, and they may change as more information becomes available.
ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker.

antihypertensive drugs should be the thiazide diuretics or the calcium channel blockers. However, it should be remembered that the majority of hypertensives require two or more drugs to achieve blood pressure control. The sequence of drugs should be as in the guidelines [34].

Fourth-line hypertensive agents

The BHS/NICE guidelines are fairly clear when it comes to the first-, second- and third-line blood-pressure-lowering drugs. However, there is no clear-cut advice onto the management of patients whose pressures are resistant to the regime of A + C + D. β-blockers retain their place as possible fourth-line agents, but this recommendation is made on the basis of no evidence. Many primary care clinicians may feel that if they have failed to control the blood pressure with three agents, then referral to a specialist for further investigation and treatment is warranted. Unfortunately, in the UK there are very few specialists in hypertension, even though this is the most common cardiovascular condition worldwide.

As evidence from clinical trials regarding the fourth-line antihypertensive agents is so limited, the choice of drugs is based on anecdote or opinion rather than evidence (Figure 4). Many physicians still feel disinclined to use β-blockers as fourth-line agents, unless there is concomitant coronary heart disease or atrial fibrillation. The role of α-blockers like doxazosin in the management of hypertension is contentious. There is only one long-term outcome trial of α-blockers in comparison with diuretics in the treatment of hypertension and this was, controversially, associated with increased incidence of heart failure [54]. Another issue is that doxazosin and other α-blockers render almost half of all women reversibly incontinent of urine [55].

There is increasing interest in the use of the nonselective aldosterone antagonist, spironolactone, in addition to an angiotensin-blocking drug in resistant hypertension. Two studies have reported good results [56,57]. Unfortunately, spironolactone causes an increase in the risk of peptic ulceration and hemorrhage and estrogenic side effects in men, leading to gynecomastia and sexual dysfunction. Amiloride causes none of these problems, but 10 mg daily is less effective than spironolactone 25 mg in resistant hypertension [58]. Both amiloride and spironolactone cause a rise in serum potassium levels, particularly in patients already receiving an ACE-I or an ARB. Clearly, if these drugs are to be used, then patients will need regular monitoring of serum sodium, potassium and creatinine levels. Eplerenone is a selective aldosterone blocker that does not have the estrogenic side effect of spironolactone [59]. It is expensive and its role in resistant hypertension is uncertain. As a result of the above problems, our concurrent practice is to use doxazosin as the fourth-line agent in men and spironolactone as the fourth-line agent in women. We regard the vasodilating β-blocker, nebivolol, as a reasonable drug to use if doxazocin or spironolactone are contraindicated or cause side effects [60].

There is almost no information on the value of the centrally acting imidazoline agonist moxonidine in resistant hypertension. Anecdotal evidence suggests it is occasionally helpful.

Dual blockade of the renin–angiotensin–aldosterone system

Some short-term, relatively small trials, mainly in diabetics with proteinuria or microalbuminuria, have suggested that adding an ARB to an ACE-I may provide extra benefits in terms of blood pressure reduction and reduction of urine protein loss [61]. However, one meta-analysis of several trials cast doubt on the value of this dual blockade of the renin–angiotensin–aldosterone system [62].

In 2008, a large major trial (ONTARGET) of the effect on blood pressure of an ACE inhibitor (ramipril) or an ARB (telmsartan) or the two drugs in combination, demonstrated only a tiny additive effect when these two agents were used together, and no added benefit in terms of the prevention of CVD [5]. Furthermore, ramipril and telmisartan were equally effective at reducing blood pressure and preventing CVD. Dual blockade of the renin–angiotensin–aldosterone system is no longer recommended for hypertension. Whilst dual blockade may reduce proteinuria more than either agent used separately, it may actually worsen the development of major renal outcomes [63].

Targets

There is only one long-term outcome trial that provides guidance as to how low we should lower blood pressure. The Hypertension Optimal Treatment (HOT) study suggested that blood pressure should be reduced to below 140/80 mmHg [64]. Unfortunately, the systolic target remains uncertain, as the HOT trial was designed to investigate the reduction of diastolic rather than systolic blood pressure. However, the anxiety that we may have been too aggressive in lowering blood pressure has largely

been allayed by the HOT study. Many clinicians might take the view that in very-high-risk patients, there might be further benefits from reducing blood pressures to below the levels validated in the HOT study. One might argue that clinicians should reduce pressures to well below the population average for the patient's age, as long as this does not cause side effects. From the epidemiological point-of-view, this approach is sound, but there is still insufficient clinical trial evidence on which to make any recommendations about lower targets. A long-term dedicated outcome trial of lowering systolic pressure in hypertensive patients to below the population average is being considered in the USA, but results will not be available for some years [65]. Several studies in high-risk patients, some of whom also had hypertension, suggest that blood pressure reduction to below the conventional target of 140/85 mmHg may further reduce cardiovascular events.

Drug side-effects

Side-effects of antihypertensive drugs are less of a problem than they were in the past. One of the reasons why β-blockers are now no-longer favored is that they cause the insidious onset of tiredness and lethargy, sleep disturbance and general fatigue. Patients often only become aware of these side-effects when these drugs are discontinued. The ACE-Is cause a cough in up to 20% of patients, particularly if they are nonsmokers [66]. The patients themselves may not be particularly bothered by the cough, and it is often the patient's partner that notices it. If a cough develops, it is reasonable to change to an ARB as these drugs do not cause cough and are remarkably free of any side effects. Life-threatening acute angioedema is a rare side effect of ACE-Is, affecting approximately 0.05% of patients. However, this side effect is four-times more common in African-origin patients [67].

The direct renin inhibitor, aliskiren, appears to have few side effects, and is about as effective as the ARBs or ACE-Is [3]. The role of this agent in hypertension is uncertain.

The dihydropyridine calcium channel blockers can cause flushing, and amlodipine, at the higher dose of 10 mg daily, causes ankle swelling in almost half of all patients. There is evidence that lercanidipine 10 mg, lacidipine 4 mg and nifedipine 30 mg cause less ankle swelling than amlodipine 10 mg [68]. The nondihydropyridine calcium channel blocker verapamil has relatively few side-effects apart from constipation. Gum hypertrophy is also a side effect of the dihydropyridines, particularly amlodipine, but is less common with diltiazem, and not seen with verapamil [69].

It is now good clinical practice to warn patients in advance of the common side effects that might occur, with information of severity and frequency. It is also worthwhile to reassure patients that any side effects that do occur are usually mild and settle on discontinuation of the drug. Patients receiving angiotensin-blocking drugs should be warned that it is important they avoid becoming dehydrated when on holiday in hot countries, or in the event of an intercurrent gastrointestinal illness. Any hypovolemia in a patient with a blocked renin–angiotensin–aldosterone system can cause a precipitate fall in blood pressure [70].

Long-term follow-up

Once the patient's blood pressure is controlled they only need to see their doctor about once a year. It is probably best that intervening consultations every 3 months or so should be with a well-trained practice nurse. There is clinical trial evidence in hospital practice that nurses achieve better blood pressure control, with a lower drop-out rate than doctors [71]. There is also an increasing view that patients should be encouraged to buy their own blood pressure machines in order to monitor their blood pressures at home. This is because home readings are more predictive of outcome than clinical 'office' readings [72]. When in doubt, 24-h ABPM may be useful. On a long-term basis it is crucial to obtain the patients cooperation in their own management. In the UK, the Blood Pressure Association (BPA) is the best patient support group available [101]. Patients should be encouraged to contact patient support groups either directly or through the website. Well-educated and motivated patients who are aware of the benefit of treatment and the hazards of uncontrolled blood pressure are more likely to comply with medication and are less likely to drop out as the years go by.

Other therapies in hypertension

The Anglo Scandinavian Outcome Trial Lipid Lowering Arm (ASCOT-LLA) convincingly showed that hypertensive patients, at relatively high cardiovascular risk, benefit from the lipid-lowering drugs even if plasma lipid levels are not raised [73]. Again, it is necessary to quantify the patient's total cardiovascular risk, and statins should be prescribed to all patients whose cardiovascular risk is greater than 20% in 10 years. In practice, almost all hypertensive patients, who also have diabetes mellitus, should be taking a statin.

The role of aspirin in hypertension remains contentious. Whilst there is a general consensus that aspirin is of value in patients who have had a cardiovascular event (stroke, transient ischemic attack or coronary heart disease), the value of aspirin in the primary prevention of these complications in hypertensive patients remains uncertain. Aspirin should not be given unless the blood pressure is well-controlled. In the HOT trial, 18,000 patients with good blood pressure control were randomized to receive aspirin or placebo [64]. The patients receiving active aspirin derived no benefit in terms of reduction in stroke. Amongst the 9000 patients who received aspirin, there was a nonsignificant reduction in total coronary events, including silent myocardial infarction. This benefit was largely offset by an excess of serious hemorrhagic events. The use of aspirin as primary prevention in hypertension therefore remains controversial.

Compliance

A great many studies show an alarming level of underconsumption of antihypertensive drugs. It is to be hoped that, with the increasing use of home blood pressure monitoring and increased education and support, patients will be more motivated to take their treatment [74]. Patients are more likely to be compliant with their medication if they feel they know the doctor or nurse who recommended the treatment and if they receive the accurate follow up [75]. Nurses can carry out almost all the maneuvers outlined in this review [71]. In both the primary and secondary healthcare settings, clear computer-based protocols should be established in order to achieve improvement in the care of hypertensive patients.

Conclusion

The understanding of hypertension and its treatment has improved considerably in recent years. However, there are still significant advances to be made. In order to achieve these, a multidisciplinary approach to the management of hypertension is necessary, involving not only primary and secondary care physicians, but also nurses, pharmacists, dieticians and, of course, the patients themselves. Whilst the optimum management of blood pressure is costly, time-consuming and often challenging, the benefits in reducing the burden of CVD are impressive. The control of hypertension prevents heart attacks and strokes. It works, and lives are being saved.

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Executive summary

- A great deal of new information regarding the management of hypertension has been published since 2000.
- The relationship between blood pressure and cardiovascular risk extends down to pressures that are below the population average
- Hypertension is the most common chronic condition requiring drug treatment worldwide.
- Clinical decisions should be made on the basis of the systolic rather than the diastolic blood pressure.
- Home blood pressures are more important than clinic readings.
- Isolated systolic hypertension, where the diastolic blood pressure is not raised, is worth treating with antihypertensive drugs.
- Antihypertensive treatment has been validated in patients over the age of 80 years.
- β-blockers are no longer recommended unless there is concurrent heart disease.
- The British Hypertension Society/National Institute of Health and Clinical Excellence recommend the ACD system for lowering blood pressure.

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