Hypertension

Neil R Poulter, Dorairaj Prabhakaran, Mark Caulfield

Raised blood pressure is the biggest single contributor to the global burden of disease and to global mortality. The numbers of people affected and the prevalence of high blood pressure worldwide are expected to increase over the next decade. Preventive strategies are therefore urgently needed, especially in less developed countries, and management of hypertension must be optimised. Genetic advances in some rare causes of hypertension have been made lately, but the aggregate effect on blood pressure of all the genetic loci identified to date is small. Hence, intervention on key environmental determinants and effective implementation of trial-based therapies are needed. Three-drug combinations can control hypertension in about 90% of patients but only if resources allow identification of patients and drug delivery is affordable. Furthermore, assessment of optimal drug therapy for each ethnic group is needed.

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International Centre for Circulatory Health, Imperial College London, London, UK (Prof N R Poulter FMedSci); **Centre for Chronic Disease Control and Public Health Foundation of India, New Delhi, India** (Prof D Prabhakaran DM); **and William Harvey Research Institute and NIHR Biomedical Research Unit in Cardiovascular Disease at Barts, Queen Mary University of London, London, UK** (Prof M Caulfield FMedSci)

Correspondence:
Prof Neil R Poulter, International Centre for Circulatory Health, Imperial College London, London W2 1LA, UK
n.poulter@imperial.ac.uk

Epidemiology

Blood pressure is a normally distributed biological variable; values at the high end of the distribution are termed hypertension. The diagnosis of hypertension is based on an arbitrary cutoff point for a measure that has a continuous and graded relation across its whole range with the risk of various cardiovascular diseases.[1] Furthermore, 50% of the disease burden attributable to high blood pressure relates to values below this arbitrary cutoff point.[2] A pragmatic definition of hypertension, proposed by Geoffrey Rose decades ago, is the level of blood pressure for which investigation and management do more good than harm. In most national and international guidelines the threshold for the diagnosis of hypertension is a systolic blood pressure measured in a clinic or office of at least 140 mm Hg, a diastolic blood pressure of at least 90 mm Hg, or both.[3–5]

The latest data from the Global Burden of Disease project show that raised blood pressure (systolic >115 mm Hg) continues to be the biggest single contributor to the global burden of disease and to global mortality, leading to 9·4 million deaths each year.[6] The effect is largely mediated through coronary heart disease and stroke; the relative risks for both these events are similar for men and women.[7] However, the relative incidence ratios of coronary heart disease and stroke deaths vary extensively by geographical location, which presumably reflects the differential coexistence of other risk factors, particularly dyslipidaemia. Furthermore, extensive data from the UK suggest that the adverse effects of systolic and diastolic blood pressure on various cardiovascular endpoints are not concordant and that their relative importance is differentially affected by age.[8]

The numbers of people affected by hypertension are predicted to rise in all regions of the world from 2000 to 2025,[9] reflecting not only that the global population is growing and ageing—and blood pressure rises with age in almost all parts of the world—but also that more than 80% of the world is deemed to be developing. Hitherto the process of development has been associated with increased exposure to the main environmental determinants of high blood pressure, such as excess intakes of salt, calories, and alcohol.

Between 1980 and 2008, the global prevalence of hypertension fell marginally in men and women.[10] However, along with numbers affected, the prevalence is expected to rise between 2008 and 2015 in all regions of the world except possibly sub-Saharan Africa, in which changes in population distribution are likely to be limited.[9]

As a consequence of the predicted increase in global prevalence of about 10%, between 2000 and 2025 an estimated 560 million extra people will be affected by hypertension.[9] This prospect is daunting, given that in 2010 high blood pressure was already the biggest single contributor to worldwide deaths.[6]

In most low-income and middle-income countries, no robust epidemiological data are available for estimates of the prevalence of hypertension at present. However, the best available data suggest that the prevalence has increased in the past two decades to rates similar to those found in high-income countries (16·0–36·9% across 12 national surveys[11]), that rates are higher in urban than in rural environments, and that treatment and control rates are low though better in women than in men.[12,13] In their review from sub-Saharan Africa, Twagirumukiza and colleagues[14] predicted a 68% increase in numbers affected between 2008 and 2015; treatment and control rates were reported to be low, as of 2008. Similarly in India, but also based on suboptimal data, a highly significant

Search strategy and selection criteria

We searched Medline and PubMed from July 1, 2009, to June 30, 2014, using various combinations of the search terms "hypertension", "blood pressure", "epidemiology", "population", "recent advances", "guidelines", "Barker hypothesis", "interuterine programming", "salt intake", "sodium intake", "reducing strategies", "genes", "blood-pressure monitoring", "developing countries", "low or low middle income countries", and "mhealth technology". We search the identified articles for additional studies of interest, some of which were over 5 years old. We filtered on quality and influence. The reference list was modified on the basis of comments from peer reviewers.

trend in prevalence across the country was apparent in men and women between 1969 and 2011; control rates were also reportedly low.[15]

Even where good epidemiological data are available, population-based and other surveys are consistent with these data from Africa and India in showing variably inadequate rates of blood-pressure control.[16,17] However, in some high-income countries, such as England and Canada, big improvements in rates of awareness, treatment, and control of hypertension have been recorded.[18,19] These improvements have occurred despite the epidemic of obesity, which is increasingly affecting younger adults and adolescents and is associated with the prevalence of not only diabetes but also hypertension, in both more and less developed countries.[11]

Overall, the prevalence of hypertension is higher in people of African origin than in those of European origin,[11] although this relation is confounded by socioeconomic status,[20] which in turn is largely explained by differences in body-mass index.[21]

An interesting observation is that as development begins in a population, high blood pressure tends to emerge in the higher socioeconomic strata, then as development progresses blood pressure evens out across the social strata until when the country is deemed to be developed, the relation inverts and low socioeconomic status is associated with higher blood pressures.[21]

Pathophysiology of blood-pressure regulation

Hypertension is generally classified as primary (essential) or secondary. Secondary hypertension generally has an earlier age at onset, no family history, and a clear cause such as a renal or endocrine disorder, or an iatrogenic trigger, such as use of oral contraceptives. Most guidelines recommend investigation for secondary causes among hypertensive patients younger than 40 years.[3–5] By contrast, primary or essential hypertension mostly arises in middle or old age as a result of interaction between lifestyle and genetic factors.

Blood pressure is a heritable trait; an estimated 30% of variance in blood pressure relates to genetic factors. Understanding of the genetic architecture of traits has progressed in rare mendelian hypertensive phenotypes, such as Gordon's syndrome (pseudohyperaldosteronism type II), which resembles human essential hypertension with middle-aged onset and thiazide responsiveness.[22] This phenotype shows the complexity of the genetics of blood pressure; four associated loci have been identified so far. The first mutations identified were in two different serine-threonine kinases affecting the sodium chloride co-transporter, which is the point of action of thiazides in the distal convoluted tubule. Two additional pathways have lately been implicated in Gordon's syndrome (Kelch 3 and Cullin); this finding effectively substratifies this rare phenotype and could provide insight for other rare diseases.[23,24] A common feature of most mendelian forms of hypertension is that they affect sodium homoeostasis and in many cases their diagnosis offers potential for stratified medicine; for example, Liddle's syndrome responds to amiloride, and glucocorticoid-remediable hypertension is responsive to steroids, which are generally more associated with high blood pressure.[22]

Advances in our understanding of the genetics of blood pressure in the population show that individual genetic loci have small effects on blood pressure (less than 1·0 mm Hg systolic and 0·5 mm Hg diastolic).[22,25–27] Genome-wide studies have now identified more than 65 loci affecting blood pressure.[22,25–27] Most of these loci include genes that would not have been expected to affect blood pressure from our knowledge of the biology of hypertension.[22] In aggregate, these genes do affect risks of stroke and coronary disease and left-ventricular structure, but they will not replace blood-pressure measurement, which assesses the combined lifestyle and genomic factors influencing blood pressure.[22,25] The discoveries so far explain only 3% of the heritability of blood pressure.[22] They have highlighted certain pathways such as the nitric oxide and natriuretic pathways and have identified several drug-treatable targets and drug repositioning opportunities to improve therapeutic options for hypertension, such as guanylate cyclase stimulators.[22]

The approach of next generation sequencing has yielded new insights into the aetiology of adrenal adenoma and Conn's syndrome, in which autonomous hypersecretion of aldosterone leads to hypertension and hypokalaemia.[28–30] Sequencing of DNA from adrenal tissue of patients with nodular adrenal hyperplasia identified two somatic gain-of-function mutations in the inward rectifier potassium channel KCNJ5 (*Kir3·4*) in about 40% of aldosterone-producing adenomas.[28–30] These mutant channels are more permeable to sodium than normal channels are, resulting in calcium influx that is sufficient to produce aldosterone secretion and cell proliferation, leading to adenoma development. Mutations in the genes encoding an L-type calcium channel (*CACNA1D*) and in genes encoding a sodium-potassium adenosine triphosphatase (*ATP1A1*) or a calcium adenosine triphosphatase (*ATP2B3*) are found in other aldosterone-producing adenomas.[28–30]

Among the most controversial suggested causes of hypertension, intrauterine programming has received continuing attention in the past few years. A review of data from experiments in animals[31] suggested that maternal undernutrition is associated with high systolic and mean arterial blood pressures, whereas raised diastolic blood pressure is associated with protein undernutrition. In reviews of observational data in human beings, the importance of preterm birth as a determinant of higher blood pressure later in life has been highlighted.[32] Data largely supportive of the hypothesis were obtained among aboriginal populations from four countries.[33] A further analysis suggested that

high birthweight was associated with higher blood pressure in younger children but low blood pressure later in life compared with children with lower birthweight.[34] Several possible mechanisms have been proposed to explain how intrauterine programming might affect blood pressure. Epigenetic modification of genes in utero, whereby regulatory regions are methylated and switched off, has been added as a potential explanation.[35]

Measurement and diagnosis

Until quite recently the diagnosis of hypertension relied entirely on measurement of blood pressure in the clinic. The accumulating body of evidence in favour of measuring blood pressure at home or by 24 h ambulatory monitoring prompted a change to the guidance from the National Institute for Health and Care Excellence (NICE) in 2011.[3] Meta-analysis of the available data comparing clinic measurement, home measurement, and ambulatory blood-pressure monitoring in diagnosis concluded that the daytime average from ambulatory blood-pressure monitoring over at least 14 measurements was better than home or clinic measurements for diagnosis or prognosis.[3] The value of ambulatory blood-pressure monitoring has been reinforced by data from the International Database of Ambulatory Blood Pressure and the Spanish Ambulatory Blood Pressure Registry.[36,37]

The effect of a 25% reduction in the diagnosis of hypertension by eliminating white-coat hypertension, coupled with fewer consultations in primary care, makes ambulatory blood-pressure monitoring cost-effective; despite the initial investment in monitors, £10 million was saved in England over 5 years.[38] The estimated prevalence of white-coat hypertension of 25% has been supported by data from Spain.[37] In addition, blood-pressure phenotypes such as nocturnal hypertension associated with sleep apnoea or masked uncontrolled hypertension are detectable only on ambulatory blood-pressure monitoring. In Ireland, a pharmacy-based service networked to a centralised registry that can handle data from any validated ambulatory blood-pressure monitor and provide an instant report to the patient is both popular among patients and informative.[39]

Home blood-pressure monitoring is increasingly used by patients. One reason why ambulatory blood-pressure monitoring was apparently superior to home blood-pressure monitoring in the 2011 NICE meta-analysis might have been the relative paucity of data from home blood-pressure monitoring. Studies of home blood-pressure monitoring published in 2014 have confirmed the prognostic value of this technique and showed that the cardiovascular risk associated with masked hypertension (normal blood pressure in the clinic and abnormal blood pressure at home) was two-to-three times higher than that for true optimal conventional blood pressure.[40,41] With the advent of affordable and accurate home blood-pressure monitoring, patients are increasingly likely to want to monitor their blood pressure at home. However, data from the Spanish Ambulatory Blood Pressure Registry showed not only that masked uncontrolled hypertension was common (over 30% among people with controlled clinic blood pressures) but also that most of this masked hypertension was due to poor nocturnal control of blood pressure.[42] This disorder is not readily detectable by home blood-pressure monitoring alone. Although simple to use smart-phone applications are now available that produce excellent and patient-accessible displays of longitudinal readings, ambulatory blood-pressure monitoring still has an important role in the diagnosis and assessment of blood pressure. A statement by the European Society of Hypertension (ESH) on the use of electronic blood-pressure measurement has reinforced the diagnostic and prognostic value of these approaches.[43]

Differences in blood pressure between arms

The 2011 NICE guidance recommends that blood pressure is measured on both arms and that the higher reading is used. This advice was reinforced by the results of a meta-analysis of the association between differences in systolic blood pressure between arms and cardiovascular outcomes; a difference of 15 mm Hg or more was associated with peripheral vascular disease, pre-existing cerebrovascular disease, and increased cardiovascular and all-cause mortality.[44]

Blood pressure variability and cardiovascular disease

On the basis of observations on the nature and timing of stroke events in relation to blood pressure in the Oxford Vascular Study,[45] Rothwell and colleagues postulated that strokes and transient ischaemic attacks were precipitated by episodic hypertension and hence blood-pressure variability rather than chronically high usual mean blood pressure. Supportive data for the hypothesis arose from several cohorts,[46–51] in which measures of long-term (visit-to-visit) variability in systolic blood pressure rather than shorter-term variability (eg, over 24 h) predicted stroke events more powerfully than did mean systolic blood pressure.

This evidence gave rise to four seminal papers published in March 2010.[52–55] They included analyses of the Anglo-Scandinavian Cardiac Outcome Trial and showed that visit-to-visit variability was the best predictor of cardiovascular events of all the blood-pressure measurements available.[52] Furthermore, the superiority of the combination of amlodipine and perindopril used in that trial for prevention of cardiovascular events appeared to result from the better effect of these drugs than of the atenolol/thiazide combination on long-term variability. A review of 389 trials suggested that drug classes exerted differential effects on blood pressure variability; calcium-channel blockers being the most effective and β blockers the least effective.[53] Although the validity of these data remains controversial, the

implications are potentially enormous for several crucial features of the clinical management of high blood pressure, including diagnosis, treatment thresholds, drug choice, and monitoring.

One striking finding among Rothwell and colleagues' analyses[52] was that episodic hypertension with a quite low mean systolic blood pressure is associated with a greater risk of a cardiovascular event than is constant hypertension with limited blood-pressure variability. The implications of these findings, if validated, would be that treatment becomes indicated for people with highly variable blood pressure, even if their mean blood pressure is quite low.

Criticisms of these analyses,[52–55] such as that raised long-term variability merely reflects heart-rate variability, poor compliance, or the use of drugs with short duration of action, appear ill founded.[52,55] Similarly, the measures of long-term variability do seem to add additional information beyond 24 h blood-pressure variability and maximum or minimum blood pressures, all of which could rationally be linked with increased risk of cardiovascular events.

If long-term blood-pressure variability is as important as the findings of Rothwell and colleagues suggest, what is needed to identify people at the high cardiovascular risk associated with this phenotype is some surrogate marker of this variability (not normally apparent at the time hypertension is diagnosed), which can be measured quickly and easily.

Management of hypertension

Diet and lifestyle

Little new information has become available in the past few years to modify recommendations on the non-pharmacological management of high blood pressure. Consequently, the most recent guidelines from USA,[56] UK,[3] and Europe[4] show very few changes from recommendations on diet and lifestyle made a decade ago[57] (table 1). However, the recommendations to reduce salt intakes, at least at the population level, have caused controversy.[58,59]

	ASH/ISH 2014[56]	ESH/ESC 2013[4]	BHS IV 2004[57]
Weight reduction	Yes	Yes	Yes
Reduction in dietary salt intake	Yes	Yes	Yes
Increase in dietary fresh fruit and vegetable intake	Yes	Yes	Yes
Increase in dietary low-fat dairy intake	Not mentioned	Yes	Yes
Physical activity*	Yes	Yes	Yes
Moderate alcohol intake	Yes	Yes	Yes
Reduction in saturated fat and cholesterol intake	Not mentioned	Yes	Yes
Regular fish intake	Not mentioned	Yes	Not mentioned

ASH=American Society of Hypertension. ISH=International Society of Hypertension. ESH=European Society of Hypertension. ESC=European Society of Cardiology. BHS=British Hypertension Society. *Endurance, dynamic resistance, and isometric resistance.

Table 1: **Non-pharmacological recommendations for reduction of blood pressure**

Some observational studies reported a J-shaped association between salt intake and risk of cardiovascular disease (increased risk at the lowest and the highest sodium intakes) or a negative association between high salt intake and risk of cardiovascular disease.[60,61] However, those studies were not designed to assess the relation between salt, blood pressure, and cardiovascular disease, and the participants were patients at high risk of cardiovascular disease or with established disease.[60–63] Thus, the studies had methodological limitations, and the results are unlikely to reflect the situation in the healthy free-living population. The 2012 review by the American Heart Association that examined these studies indicated that the evidence relating to the adverse health effects of excess salt intake remains strong, with no need for current recommendations on reduction in salt intake to be changed.[64]

Data from a large observational study of 51290 people supported a direct association between high sodium intake and high blood pressure.[65] However, substantial heterogeneity was apparent, depending on hypertension status and age in the effects of sodium on blood pressure. At low sodium intakes and among young and normotensive individuals, the effects of sodium on blood pressure were small, which suggests that very low sodium intakes might not be beneficial. However, urinary sodium excretion was measured by spot urine assessment, and the correlation between this simple measurement method and blood pressure is poor. Furthermore, reverse causality is a possibility. Nevertheless, the results of the analysis of salt intake in relation to mortality and cardiovascular events in this study suggested a J-shaped relationship.[66]

Despite polarised views on the harm or otherwise of salt, a reasonable consensus based on a credible body of current scientific evidence and supported by WHO and other leading health organisations is to recommend a daily salt intake of 5 g or less.[67,68] Most national and international guidelines and position statements for cardiovascular disease prevention and control universally recommend dietary salt reduction as an important strategy to prevent hypertension and associated cardiovascular disease in both hypertensive and normotensive individuals.[67,69] Given the potential of reduction in salt intake as an intervention for reducing hypertension and cardiovascular disease, the United Nations and WHO global targets for chronic disease reduction include a 30% relative reduction in population-level salt intake by 2025.[70] We believe this target remains reasonable despite the recent controversies.

Pharmacotherapy of hypertension

Despite the extensive list of major morbidity and mortality trials of antihypertensive agents,[71] management guidelines, which presumably refer to the same database, remain inconsistent in terms of key areas of hypertension management. For example, within Europe, the latest European guidelines[4] differ fundamentally with those from the UK[3] in drug selection. The European guidelines

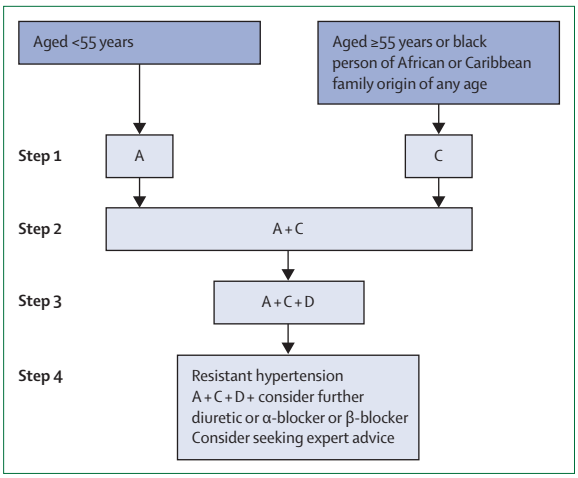

Figure: **Summary of selection and sequencing of antihypertensive drugs**
A=ACE inhibitor or angiotensin-receptor blocker. C=calcium-channel blocker. D=thiazide-like diuretic. Adapted from NICE hypertension guidelines (2011),[3] with permission.[3]

	Recommended drug combinations
NICE[3]	A + C
ESH ESC[4]	A + C, A + D, C + D
ASH-ISH[56]	
Black	A + C, A + D, C + D
Non-black	A + C, A + D
JNC8[5]	
Black	C + D
Non-black	A + C, A + D, C + D

NICE=National Institute for Health and Care Excellence. ESH=European Society of Hypertension. ESC=European Society of Cardiology. ASH=American Society of Hypertension. ISH=International Society of Hypertension. JNC8=Eighth Joint National Committee. A=ACE inhibitor or angiotensin-receptor blocker. C=calcium-channel blocker. D=diuretic (including thiazides or thiazide-like/type).

Table 2: **Recommended two-drug combinations of antihypertensive drugs**

do not prioritise the drug classes as first-line agents, whereas the UK guidance[3] takes a different, simplified view (figure). The continued promotion of β blockers as first-line agents in the European guidance is surprising in light of several reviews,[72,73] but closer scrutiny of the document shows that this class is recommended only for subgroups of patients when compelling indications prevail, such as angina, heart failure, or atrial fibrillation, and after myocardial infarction. The proposed use of β blockers (as opposed to labetalol) in pregnancy is questionable[74] and in aortic aneurysm has little supportive data.[75] Indeed, given suboptimal effects of β blockers on central blood pressure[76] and blood-pressure variability,[53,55] this drug class could actually be an inappropriate choice in aortic aneurysm with possible advantages of renin-angiotensin system blockade.[77]

The long-awaited report of the Eighth Joint National Committee (JNC8) was finally published in 2014,[5] but only independently by some members of the Committee initially appointed to it.[5] This publication was preceded by two other conflicting documents involving major societies from the USA and elsewhere.[56,78] The first of these[78] made no apparent attempt to be evidence-based or to address many of the key issues normally included in hypertension guidelines. However, the statement by the American Society of Hypertension and the International Society of Hypertension (ASH/ISH)[56] and the JNC8[5] report both moved towards UK guidance[3] in that they differentiated therapy allocation on the basis of age (albeit inconsistently) and ethnic group. Although the guidelines differ in terms of recommended combinations of therapy (table 2), the recommendations made are essentially variations on any two of renin-angiotensin system blocker, calcium-channel blocker, and diuretic. The logical, if controversial,[79] drug sequencing promoted by NICE (figure) is one of very few algorithms included in any national or international guidelines that provides simple step-by-step guidance on how to manage increasingly resistant hypertension.

One of the more contentious features of the NICE guidance on drug selection[3] was the positive discrimination in favour of indapamide or chlortalidone (thiazide-like diuretics) as opposed to thiazide diuretics. This recommendation was based on meta-analyses of the inferior blood-pressure-lowering efficacy of low-dose thiazides compared with other drug classes over 24 h[80] and compared with other diuretics.[81,82] More importantly, the three morbidity and mortality trials that compared low-dose thiazides (equivalent to ≤25 mg hydrochlorothiazide) all found that the comparator drug was superior.[51,83,84]

By contrast, evidence from morbidity and mortality trials is available to support the use of indapamide[85–88] and chlortalidone[89–92] and higher-dose thiazides.[93–98] The higher-dose thiazides have fallen out of favour owing to adverse metabolic effects (even when potassium supplementation or sparing agents are added) and hence indapamide and chlortalidone remain as the diuretics recommended in the NICE guidelines.[3]

The conflicting classification of diuretics used across the guidelines is somewhat confusing. ASH/ISH[56] and ESH[4] recommended thiazides (which actually means thiazides or thiazide-like diuretics), the JNC8 Committee[5] recommended thiazide-type diuretics (which also actually means thiazides or thiazide-type diuretics). The NICE[3] guidelines differentiate thiazide-like from thiazide diuretics, preferring the former to the latter.

The latest European guidelines[4] propose the use of two drugs in combination to initiate therapy for a large proportion of patients, as did the ASH/ISH statement,[56] although JNC8[5] was less prescriptive about this approach than the seventh JNC was.[99] Although this approach seems logical and appropriate, it remains largely unsupported by evidence from randomised studies,[100] although data from large observational studies do provide support.[101,102]

Guidance on the use of single-pill combinations of drugs (commonly but inaccurately referred to as fixed-dose combinations) is similarly variable across the

guidelines. What evidence is available suggests: that the use of single-pill combinations of two antihypertensive agents is associated with substantially better adherence than for the same two agents given separately;[103] that patients started on single-pill combinations experience better blood-pressure control than patients started on monotherapy or two drugs given separately;[101] that initiation with single-pill combinations provides significantly better cardiovascular protection than initiation with monotherapy;[104] and that the use of single-pill combinations is a more cost-effective treatment approach than the use of free drug combinations.[105,106] Despite the lack of compelling randomised trial evidence for the use of single-pill combinations, the British Hypertension Society (BHS) recommendation of 2004[57] to use single-pill combinations as long as there is no cost disadvantage and the NICE suggestion that "simplifying the dosing regimen" by use of single-pill combinations might improve adherence[3] should probably be strengthened to recommend the use of single-pill combinations where they are available, unless there are clear indications (eg, large cost differentials) for separate administration of medications. Although ideally necessary, more definitive trial evidence to support or refute the use of single-pill combinations will probably remain elusive since the benefits of their use are likely to depend on the size of the price differentials, which vary widely around the world.

The European guidelines of 2013[4] and subsequently ASH/ISH[56] and JNC8[5] in 2014 differ from most others produced before 2013 in taking a conservative approach to blood-pressure targets. Previously, almost all guidelines were consistent in suggesting a target of 130/80 mm Hg or lower for all patients with diabetes or chronic renal failure.[57,99,107] Since no good robust evidence for these targets in these two groups of patients is available, the targets recommended have been raised to 140/85 mm Hg and 140/90 mm Hg, respectively. These more conservative targets reflect a more conservative threshold of 140/90 mm Hg for all patients irrespective of risk,[4] compared with those recommended in 2007[107] and 2009.[108] This decision partly reflects acknowledgment of a paucity of robust data to inform good decisions on when to initiate therapy but also of some observational post-hoc evidence, which rightly or wrongly introduced concerns about a J-shaped effect on cardiovascular outcomes associated with lower blood pressures among some subgroups of patients.[109–111]

The most surprising recommendation on blood-pressure treatment thresholds and targets arises from the JNC8 guidelines,[5] in which for patients aged 60 years and older (most of the hypertensive population) the treatment threshold has become more than 150/90 mm Hg and the blood-pressure target has become less than 150/90 mm Hg. This recommendation was classified as "Grade A, Strong", but it conflicts with those from ESH/ESC,[4] ASH/ISH,[56] and NICE.[3] The six trials that reportedly generated the strength of this recommendation include four trials of isolated systolic hypertension and two described as low quality; why a cutoff point of 60 years was chosen in JNC8 was not clear from any of the trials. The conclusions drawn from these six trials seem at odds with the only other systematic review of these data[3] and other larger compilations of trial evidence[71,112] and they have been challenged by some of the original JNC8 committee members.[113]

Resistant hypertension probably affects about 1 million people in the UK, on the basis of assumptions from the Health Survey for England.[18] This number corresponds to about 8% of the hypertensive population in the UK. However, the estimate almost certainly exaggerates the proportion because individuals who do not adhere to treatment or use suboptimal combinations and doses of drugs, and those with undiagnosed secondary causes of hypertension were not excluded from the 8%. Very useful new methods based on mass spectrometry of urine can assess whether patients are actually taking their medicines and have suggested that non-adherence is directly proportional to the number of medications being taken.[114] Furthermore, the addition of spironolactone as a fourth-line agent[115] (as recommended initially by the 2011 NICE guideline[3] and subsequently in ASH/ISH[56] and JNC8 guidelines[5]) should probably be incorporated into the routine treatment algorithm before resistance is diagnosed. The British Heart Foundation/British Hypertension Society PATHWAY research programme is exploring the optimum regimen for resistant hypertension.[116]

Device-based therapy for hypertension

Sympathetic drive has long been a therapeutic target in hypertension, but selective renal denervation is an innovative tactic. One approach involves administering radiofrequency energy to the wall of the renal artery with the intent of disrupting renal sympathetic afferents signalling the brain. In 2010, a randomised controlled trial without a sham procedure showed that in individuals with severe resistant hypertension, uncontrolled by three or more agents, renal denervation lowered blood pressure by an average of 33/11 mm Hg.[117] These findings led to national and international guidance,[118,119] great enthusiasm to use the procedure, and many devices in development. In a large, more definitive randomised trial of renal denervation including a sham procedure (Symplicity HTN3) the modest blood-pressure-lowering endpoints for both clinic blood pressure and ambulatory blood-pressure monitoring were not met.[120] Several factors could have contributed to this negative result.[121] Until the results of further research focused on patients with potentially susceptible phenotypes and including sham procedures and routine spironolactone use balanced between the trial groups are available, the place for renal denervation in clinical practice remains uncertain and should probably be restricted to research in randomised trials.

Other approaches being investigated for a role in resistant hypertension include carotid baroceptor stimulation, in which an electrode is attached to the carotid sinus and a small battery is tunnelled under the skin on the anterior chest wall as for a pacemaker.[122,123] After the chance finding that a shunt from the small iliac artery to vein, created with the aim of improving breathlessness in chronic obstructive pulmonary disease, also lowers blood pressure, this shunt is now being formally studied as a potential hypertension treatment.[124]

Prevention and management in developing countries

The processes whereby populations are deemed to be more developed have inexorably been associated with rising mean blood pressures and increasing rates of hypertension. This association is hardly surprising since with development comes increasing longevity, excess intake of salt, alcohol, and saturated fats, and reduced exercise and intake of fresh fruit and vegetables. However, an opportunity is available to intervene in populations that are in the early stages of development with a view to preventing the rise of blood pressure with age and hence the development of hypertension, which in developed countries affects most people after the age of 50 years.[2,9,18]

Since developing countries also have a huge burden due to hypertension, occurring at younger ages than in more developed countries, special attention and innovations are needed to prevent and manage hypertension. Barriers to the optimum prevention and management of hypertension in developing countries include inadequate access to health care, insufficient and inadequately trained health-care workforces, uneven distribution of health-care providers with more physicians in urban than in rural locations, emphasis on curative care over prevention, and the lack of clear locally relevant clinical management guidelines. To combat the hypertension burden, many innovative approaches are needed; they include task-shifting or task-sharing to address the shortage of health workers to improve detection and screening of hypertension through front-line staff; easing work flow at health-care facilities; and use of simple and ubiquitous technologies such as mobile phones or tablet devices as electronic clinical decision support tools.

Task-shifting or task-sharing—delegation or sharing of tasks from physicians to less-specialised, non-physician health workers such as nurses and pharmacists—is a possible solution to the shortage of manpower.[125] Task-shifting has been successfully demonstrated in scaling up of interventions in chronic infectious diseases such as HIV/AIDS and found to be feasible in the management of disorders such as hypertension and diabetes and reducing cardiovascular risk.[126–130] These encouraging research findings offer hope for task-shifting in expanding hypertension care in resource-limited places.

Use of technology to aid in clinical decision support for non-physician health workers in public health is gaining impetus as a potential solution to prevent or reduce medical errors in the absence of close supervision by physicians. Electronic medical records and computerised clinical decision-support systems are increasingly being used to promote evidence-based care in the primary-care setting. A systematic review of such interventions found that computerised clinical decision-support systems along with an information-technology-assisted management programme had significant effects on systolic blood pressure in patients with hypertension.[131] With the advantages of portability and communication and computing capabilities, smartphones are judged to be an alternative to computers as a useful tool in expanding health care in developing countries. A systematic review of controlled trial interventions based on mobile-phone technology for health-care delivery processes found small benefits in diagnosis and management outcomes in several health conditions.[132] Similarly, benefits were also shown with self-monitoring of blood pressure and bodyweight in a weekly web-based diary through the internet or by cellular phones along with remote support from the clinic facilities in a quasi-experimental design.[133] Although research evidence is mostly from more developed countries, rapid expansion of mobile phone infrastructure even in remote areas of less developed countries has opened up the possibilities of equipping non-physician health workers with smartphone tools for hypertension care. Large trials are needed of electronic clinical decision-support devices used by non-physician health-care providers (front-line health workers or nurses) on major cardiovascular events in patients with hypertension.

Panel 1: **Research recommendations, NICE 2011[3]**

- In adults with primary hypertension, does the use of out-of-office monitoring (home blood-pressure monitoring or ambulatory blood-pressure monitoring) improve response to treatment?
- In people aged under 40 years with hypertension, what are the appropriate thresholds for intervention?
- In people aged under 40 years with hypertension, what is the most accurate method of assessing the lifetime risk of cardiovascular events and the effect of therapeutic intervention on this risk?
- In people with treated hypertension, what is the optimum systolic blood pressure?
- In adults with hypertension, which drug treatment (diuretic therapy *vs* other step 4 treatments) is the most clinically effective and cost effective for step 4 antihypertensive treatment?
- Which automated blood-pressure monitors are suitable for people with hypertension and atrial fibrillation?

Panel 2: **Gaps in evidence and need for future trials: ESH-ESC guidelines 2013[4]**

- Should antihypertensive drug treatment be given to all patients with grade 1 hypertension when their cardiovascular risk is low to moderate?
- Should elderly patients with systolic blood pressure between 140 and 160 mm Hg be given antihypertensive drug treatments?
- Should drug treatment be given to individuals with white-coat hypertension? Can patients with this condition be differentiated into those needing and those not needing treatment?
- Should antihypertensive drug treatment be started in the high normal blood pressure range and, if so, in which patients?
- What are the optimum office blood pressures (ie, the most protective and safe) for patients to achieve by treatment in different demographic and clinical conditions?
- Do treatment strategies based on control of out-of-office blood pressure provide an advantage (reduced clinical morbidity and mortality, fewer drugs, fewer side-effects) over strategies based on conventional (office) blood pressure control?
- What are the optimum out-of-office (home and ambulatory) blood pressures to be reached with treatment and should targets be lower or higher in hypertensive patients at high risk?
- Does central blood pressure add to prediction of cardiovascular events in patients with untreated and treated hypertension?
- Do invasive procedures for treatment of resistant hypertension compare favourably with the best drug treatment and provide long-term blood-pressure control and reduction of morbid and fatal events?
- Do treatment-induced changes in asymptomatic organ damage predict outcome? Which measures—or combinations of measures—are most valuable?
- Are lifestyle measures known to lower blood pressure able to reduce morbidity and mortality in hypertensive patients?
- Does a treatment-induced reduction of 24 h blood-pressure variability add to cardiovascular protection by antihypertensive treatment?
- Does blood-pressure reduction substantially lower cardiovascular risk in resistant hypertension?

Missing research

The NICE 2011 guidelines[3] and the latest European guidance[4] (panels 1 and 2) drew attention to the main areas for which evidence is limited—particularly blood-pressure targets and thresholds in subgroups of patients. To address these gaps in the evidence base, two trials have been initiated. The first is the Systolic Blood Pressure Intervention Trial (SPRINT), which will compare the effect on various cardiovascular and cerebrovascular endpoints of two strategies for treating systolic blood pressure in 9361 patients with the standard systolic pressure target of below 140 mm Hg and a more intensive target of below 120 mm Hg in individuals older than 50 years with an average baseline systolic blood pressure of at least 130 mm Hg and evidence of cardiovascular disease or chronic kidney disease.[134] The second is the Stroke in Hypertension Optimal Treatment (SHOT) trial, organised by the ESH and the Chinese Hypertension League. It is a prospective multinational, randomised trial of three different targets for systolic blood pressure and two different targets for LDL-cholesterol concentration in the prevention of stroke, cerebral function, and other cardiovascular events.[135] The trial will include 7500 patients aged at least 65 years who have hypertension and have had a stroke or transient ischaemic attack 1–6 months before randomisation. The need for more evidence on the value of home, central, and ambulatory blood-pressure measurement is also highlighted.

One omission from both sets of guidelines is an issue that was raised in the WHO-ISH guidelines of 1999.[136] These 1999 guidelines recommended nine areas for further research, and progress has been made on all but one or two of these topics. The outstanding issue is hypertension in developing countries. Variations in responses to different antihypertensive agents in different ethnic groups are well known.[92] The hypertension research community must address the fact that most cases of hypertension around the world are in individuals from ethnic groups for which little or no trial evidence on optimal treatment is available.[137] A few trials have been done in which oriental populations predominated or were the sole participants[85,86,88,138,139] but none have compared optimal first-line or two-drug combinations. The situation is similar for major morbidity/mortality trials in black patients of African origin.[92,140] However, essentially no major outcome trials have been done in which South Asian patients represented even a reasonably sized subgroup.

A crucial development therefore is that robust randomised trial data are generated on which antihypertensive medications are most effective by ethnic subgroups, initially at least in terms of lowering of blood pressure, but ultimately data on major outcomes are also required.

Contributors

NRP provided the initial outline and draft of the Seminar and he provided and coordinated responses to referees and the report revision. DP and MC provided intellectual input into the development writing and editing of the Seminar; they assisted on responding to referees and participated in the report revision.

Declaration of interests

NRP reports having received grants from Pfizer and Servier, and payment for lectures from several pharmaceutical companies producing blood-pressure lowering, glucose lowering, and lipid lowering drugs such as Menorini, Sevier, Daiichi Sankyo, Boeringer-Ing, Takeda, Medtronic; and he is Chairman of the BHS Guidelines & Information Service Working Party and Member of the ISH Executive Committee. DP is a member of the Executive council of International Society of Hypertension. MC is the Chief scientist for Genomics England; he has received honoraria for lectures from Medtronic.

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