Controversies in Cardiology 2

Controversies in hypertension

Norman M Kaplan, Lionel H Opie

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This is the second in a Series of four articles on controversies in cardiology

University of Texas Southwestern Medical Center, Dallas, TX, USA (Prof N M Kaplan MD); and Hatter Institute for Heart Research, Cape Heart Centre and Department of Medicine, University of Cape Town Medical School, Observatory 7925, South Africa (Prof L H Opie FRCP)

Correspondence to:
Prof L H Opie
norman.kaplan@utsouthwestern.edu

Hypertension remains the most common risk factor for cardiovascular morbidity and mortality. Its incidence is rising in both ageing and obese populations, but its control remains inadequate worldwide. We address several persisting controversies that may interfere with appropriate management of hypertension. They include: the reasons behind the increasing incidence of hypertension and the possible ways to slow the process, especially by lifestyle changes; the need for overall cardiovascular risk assessment; the major issues in the decision to institute drug therapy and the choice of drugs; and the importance of screening for various identifiable causes. We provide the background for these controversies, followed by some opinions on how to guide practitioners to offer more effective management of hypertension.

Hypertension remains the most common risk factor for cardiovascular morbidity and mortality (figure 1).[1] Despite massive and costly efforts to identify and treat hypertension, less than a third of individuals with a usual blood pressure exceeding 140/90 mm Hg are adequately treated.[2,3] Even in individuals whose hypertension is thereby presumed to be well controlled, less than a third are protected from subsequent strokes and heart attacks.[4,5] The inadequacy of current practice is obvious: too few individuals at risk, because of raised blood pressure, are being diagnosed and treated effectively. Another reason is the complexity of the origin of hypertension, a multifactorial disease (figure 2).[6] Therefore, much improved population-wide and individual approaches to the prevention and control of hypertension are needed. Here, we address selected controversies of hypertension, along with some of our views on how doctors should provide the best management.

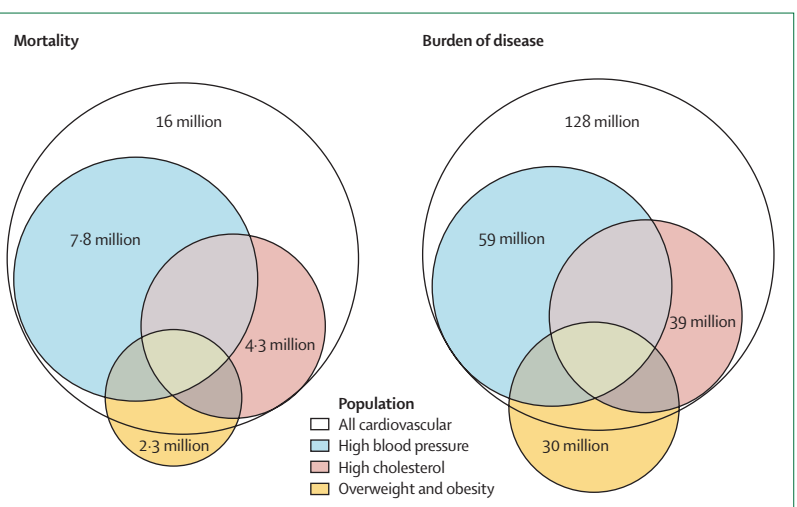

Figure 1: **Global mortality and burden of cardiovascular disease and major risk factors for people aged 30 years**
Reproduced from reference 1, with permission.

Search strategy and selection criteria

We searched MEDLINE or PubMed with hypertension as key word and combinations with cardiovascular disease, lifestyle modifications, weight loss, antihypertensive drug therapy, and identifiable or secondary causes. We specifically searched major hypertension journals including: *The Lancet, British Medical Journal, New England Journal of Medicine,* and *Circulation* for similar or related articles.

Developing countries and increasing incidence of hypertension

"More than a quarter of the world adult population is already hypertensive and this number is projected to increase to 29%, 1·56 billion, by 2025."[7] Almost three-quarters of the worldwide population with hypertension will be in developing countries, with this occurrence fuelled by urbanisation. Thus, global-health inequalities will be further increased. Therefore, attention should be directed at possible ways to slow this occurrence through population-wide manoeuvres, including the avoidance of obesity, increased exercise, and reduction of dietary sodium.[8] But how can any of these become a national priority in developing countries when other diseases such as HIV/AIDS must take priority for restricted health budgets, along with the ravages of persistent infectious diseases, famine, drought, and civil strife? These factors will dominate over apparently non-urgent health priorities such as hypertension, at least in sub-Saharan Africa. Thus global approaches need to focus on lifestyle changes that can be widely initiated as preventive measures, whereas approaches for individuals should be associated with antihypertensive drug therapy. How can these aims be best achieved?

Can the prohypertensive trends of urbanisation be modified?

Presumably multigenic, the occurrence of persistent hypertension is increased by the following common environmental factors: excessive dietary sodium, weight gain from increased caloric intake plus physical inactivity, excessive alcohol intake, and excess psychological stress. Of these factors, weight gain is

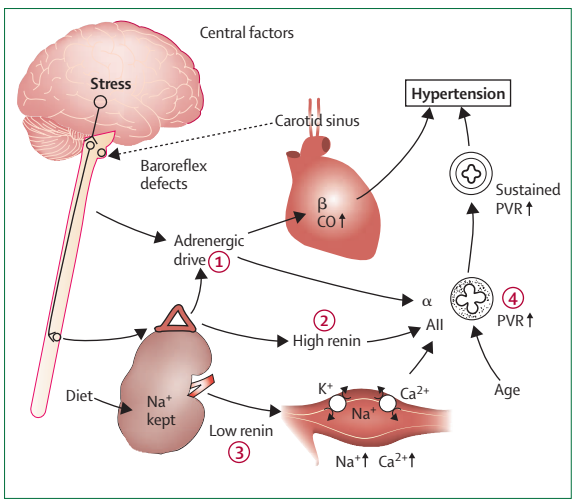

Figure 2: **Multifactorial origin of hypertension**
Major mechanisms: (1) increased adrenergic drive, as often found in young people (aged 30–49 years); (2) high-renin hypertension, as seen in individuals with renal dysfunction; (3) low-renin hypertension, as recorded in individuals with inherently raised aldosterone concentrations; (4) increased peripheral vascular resistance (PVR), as seen in elderly patients. CO=cardiac output. β=β-adrenergic stimulation. α=α-adrenergic stimulation. AII=angiotensin II. Adapted from reference 6, with permission.

increasing most rapidly in both developed and developing societies, other than for societies with persistent inadequacy of food. With urbanisation, black South Africans undergo a nutritional transition from traditional, rural, carbohydrate food with a low glycaemic index to a diet high in fat and poor-quality carbohydrate fast-foods.[9] The result is that 58·5% of South African black women are overweight or obese, with some women's shapes augmented by the culturally desirable value of obesity.

A comprehensive population-based approach can achieve goals to reduce the frequency of hypertension, and Cuba could be a good model.[10] Lifestyle changes are actively promoted by the media with a female obesity rate of about half that in South Africa, with a high standard of awareness and hypertension treatment provided by a well-developed health-care system. Physical activity is high, because of the daily use of bicycles. At the other economic extreme, in the USA, despite increasing obesity and inactivity, a low prevalence of hypertension (figure 3)[11] and low stroke rate exists compared with some European countries.[3] These differences could indicate the increased attention paid to active drug treatment, leading to higher control rates of hypertension in the USA than in Europe.[3]

Opinion

A general nationwide policy contrasts with that for the individual; reduction of the blood pressure of the whole population by 2 mm Hg would give more overall benefit than much larger individual reductions focused on only a few people. Therefore, the global aim should focus on the implementation of lifestyle changes rather than personal drug therapy.

Which lifestyle changes are effective?

(1) How effective are comprehensive lifestyle changes?

In a US trial of overweight people with prehypertension and people with stage 1 hypertension not on drug therapy, all with initial mean blood pressures of 134/85 mm Hg, researchers tested lifestyle changes over 6 months.[12] The measures were weight loss, reduced dietary sodium and alcohol intake, and increased exercise. Overall, bodyweight fell by 4·9 kg, fitness improved, urine sodium values fell by 32 mmol per day, and blood pressure fell by a mean of 3·7/1·7 mm Hg lower than values in the control group. However, these individuals were highly motivated volunteers who were willing to make lifestyle changes and who were subjected to constant personal effort and encouragement from various professionals.[13] Lesser results can be expected if strong motivation is absent in either patient or doctor.

(2) Does weight loss reduce blood pressure?

Overall, a 10-kg weight loss achieved by non-surgical means and sustained for 2 years is accompanied by a mean fall of 6·0/4·6 mm Hg in blood pressure.[14] Even greater reductions in bodyweight that are achieved by gastric bypass with biliopancreatic diversion provide increased falls in blood pressure,[15] whereas gastric banding procedures have little persistent effect.[16]

(3) Do popular diets help to control blood pressure?

Promoters of various diets create undue optimism, which is essential for their massive financial success. In reality, there is "sparse scientific evidence behind the

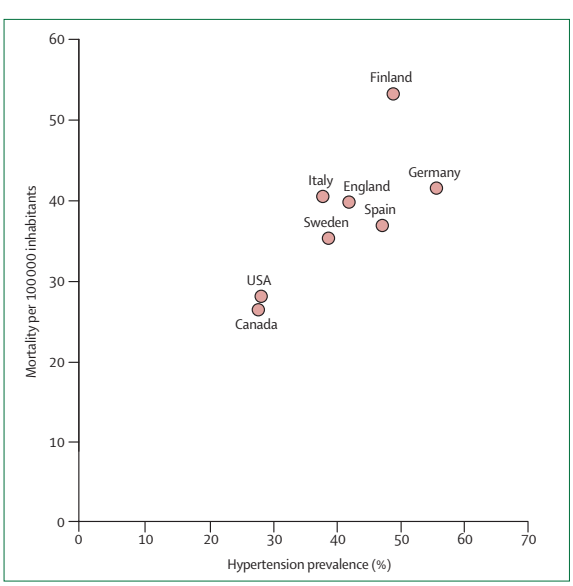

Figure 3: **Prevalence of hypertension in various countries**
Reproduced from reference 11, with permission.

claims made for the leading diet plans".[17] Thus, diets from Atkins to the Zone have low adherence rates (about 25% over 1 year) and could achieve little weight loss with negligible changes in blood pressure.[18] Nevertheless, such calorie-reduced diets might (if adhered to) modify cardiovascular risk factors, including blood-pressure reduction. Notably, in two studies, diet combined with sodium restriction successfully reduced blood pressure, with a greater decrease at 21 weeks[19] than at 52 weeks.[20]

(4) Do weight-reducing drugs reduce blood pressure?

Orlistat treatment for 4 years, together with lifestyle modifications, reduced bodyweight by 5% and blood pressure by 4·9/2·6 mm Hg (from initial values of 130·8/82·0 mm Hg), compared with a fall of 3·5/1·9 mm Hg with lifestyle alone ($p<0·01$).[21] With the newest drug, the cannabinoid-1-receptor blocker rimonabant, a daily dose of 20 mg reduced the blood pressure of obese individuals with hypertension by a mean of 13·1/6·3 mm Hg versus 7·2/2·4 mm Hg in controls ($p=0·038$), with both groups receiving a hypocaloric diet for 12 months.[22]

(5) Does exercise help reduce blood pressure?

As a standard part of lifestyle change, regular aerobic exercise in individuals with hypertension was associated with an average fall in blood pressure of 4·9/3·9 mm Hg.[23] Moreover, exercise combined with at least a 7% weight loss reduced the onset of new diabetes, such that 6·9 people exercising for 3 years could avoid one new case of diabetes.[24] Notably, intensive one-to-one counselling was given to reinforce behavioural changes.

(6) How successful is sodium restriction?

Moderate dietary sodium restriction from the usual 150 mmol per day to 80 mmol per day will reduce blood pressure by about 5/3 mm Hg in individuals with hypertension, according to a meta-analysis of 28 trials.[25] A similar sodium reduction in isolated systolic hypertension resulted in a reduced systolic blood pressure by about 10 mm Hg.[26] In the Dietary Approaches to Stop Hypertension (DASH)-sodium study,[27] further sodium chloride restriction to 65 mmol per day enhanced the blood-pressure-lowering benefits of the high-fruit, high-vegetable, DASH diet, which led to a reduction of about 7 mm Hg lower systolic blood pressure than that with the control high-sodium diet.

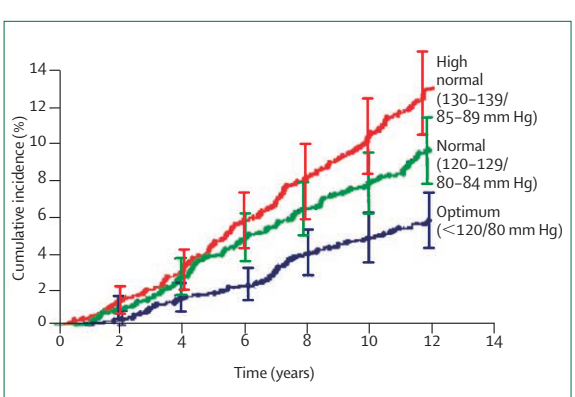

Figure 4: **Cardiovascular events in men with high-normal blood pressure**
Data are means and error bars are SDs. The event rate pattern in women is similar to that of men, but the rate is reduced. Reproduced from reference 29, with permission.

Opinion

Improved awareness of the multiple adverse consequences of obesity, physical inactivity, and excessive sodium intake should lead to concerted societal efforts toward prevention. However, the allures of fast-foods and reduced physical activity that accompany urbanisation may be impossible to overcome. Thus, in reality, obesity will probably continue to rise and the accompanying obesity-related hypertension will continue to be a problem. Comprehensive modification of lifestyle including diet, increased exercise, and decreased sodium intake does reduce blood pressure, but needs substantial personal effort to sustain. However, in societies with well-organised comprehensive health systems such as Cuba, Australia, and some European countries, lifestyle changes (such as prevention of obesity and increased exercise) could be combined with community awareness and low-cost medical care to reduce prevalence of blood pressure and to achieve improved control. Furthermore, in a society where the sodium content of food is clearly labelled, sodium restriction is the simplest measure to apply.

Risk factor assessment

More than 50 years ago, George Pickering (then Regius Professor of Medicine at Oxford University, UK) stated that no single dividing line exists between normotension and hypertension. Despite the need for admittedly arbitrary divisions to guide diagnosis and therapy, Pickering's wisdom has been repeatedly authenticated.[28] With the recognition that risk increases linearly even in high-normal ranges in blood pressure (figure 4),[29] the need for assessment going beyond blood pressure values and using individuals' absolute overall cardiovascular risk as the criterion for therapy has become obvious.[30] Therefore, should calculation of risk of future cardiovascular events and mortality replace blood pressure values per se as signals for institution of drug therapy? Theoretically, these factors can be combined, but in practice they could conflict greatly. According to risk-factor predictions, a 50-year-old woman with a blood pressure of 180/100 mm Hg and no other risk factors should not be given drug treatment, since she only has a 5-year cardiovascular disease risk of 3%. However, such risk factor calculations do not allow for subtle but important changes in cognition, the inevitable effects of sustained

high blood pressure on renal function, left-ventricular hypertrophy with diastolic dysfunction and risk of atrial fibrillation, or arterial damage. Moreover, additional risk factors such as abdominal obesity, microalbuminuria, raised C-reactive protein, or hyperuricaemia (now not included in cardiovascular risk assessments), could provide a more accurate profile.[31]

Opinion

Risk-factor calculation is essential for the determination of the overall effect of hypertension and the cost-effectiveness of therapy, whereas blood pressure values should still be used with respect to individual patients. Therapy guidelines can combine these approaches, such as those of the British Hypertension Society, which recommends drug therapy for individuals with a blood pressure of 160/100 mm Hg or more (with much lower limits for patients with diabetes), and risk-factor calculations for those between 140/90 mm Hg and 160/100 mm Hg or more.[32] Various risk scores are available, but the Framingham model is the most widely advocated, and applies in principle to other populations.[33]

Ageing and hypertension

The systolic blood pressure increases with age as the aorta stiffens (figure 5),[6] so that 90% of Americans still having a healthy blood pressure at age 55 years will have hypertension when they reach age 75 years.[34] This systolic upswing is worldwide.[2] Can this process be avoided? Indirect evidence shows that the rise in blood pressure is related to urbanisation and a modern lifestyle. Unacculturated societies, such as the San bushmen in southern Africa, or protected groups, such as nuns living in a convent, have blood pressure that do not increase with age.[35] Which are the crucial lifestyle changes that are needed to avoid this inevitable rise? The San bushmen and nuns have very little in common, apart from being a very tightly knit society and isolated conditions. For most, the stresses of modern life are difficult to avoid.

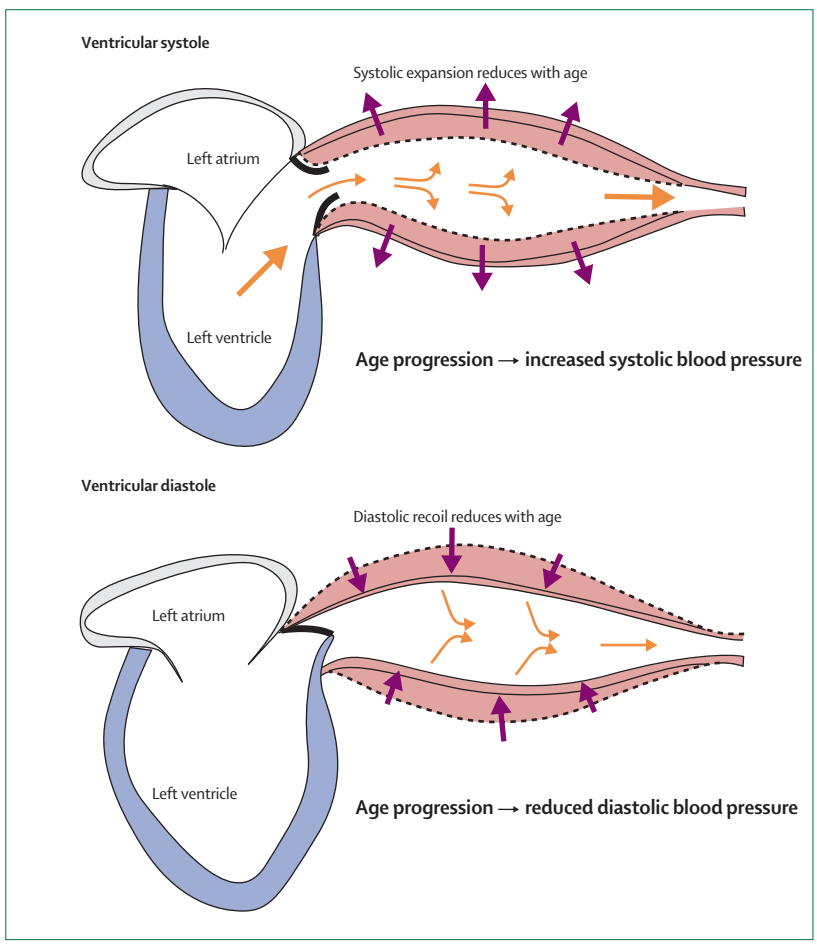

Figure 5: **Role of aortic compliance on blood pressure and effect of ageing**
During ventricular systole, the stroke volume ejected by the ventricle results in some forward blood flow, but most of the ejected volume is stored in the elastic arteries. This process represents the healthy pressure-equalising or buffering function of the aorta. During ventricular diastole, the elastic recoil of the arterial wall maintains blood flow for the rest of the cardiac cycle. With ageing, the stiffened aorta increases the systolic blood pressure, while the loss of elasticity decreases diastolic recoil so that the diastolic blood pressure falls. Adapted from reference 6, with permission.

Blood-pressure reduction: does one size fit all?

Two meta-analyses of the multiple randomised controlled trials that closed before mid-2003[4,5] came to the same conclusions: (1) blood-pressure reduction by any drug compared with placebo reduced cardiovascular morbidity and mortality; (2) all classes of drugs reduced total and cardiovascular mortality equally; and (3) different classes provided differing degrees of protection against individual cardiovascular morbidities. Specifically, the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) study[36] compared three initial therapies: diuretics, calcium-channel blocker, and angiotensin-converting-enzyme (ACE) inhibitors, and showed no difference between treatments on fatal coronary heart disease, non-fatal myocardial infarction, or all-cause mortality. Hence, most national and international guidelines recommend initial diuretic therapy, even though the incidence of diabetes rose in the diuretic group of ALLHAT and the adverse effects of such drug-induced diabetes might take several more years to become overt.

Since the review by Staessen and colleagues,[5] several other randomised controlled trials have been completed that examined the effects of various drugs (either against placebo or another active drug), mostly in patients with coronary disease of various degrees of stability.[37] Most patients in these trials had hypertension, but their blood pressure was generally well controlled on various drugs other than those being tested. In most trials comparing different classes of drugs, small but clinically significant differences in blood pressure were seen, which probably contributed to the possible advantage of one substance over another.

	Duration (years)	New diabetes (%)/ comparator regimen	New diabetes (%)/ combination regimen	Relative risk (95% CI)	p
ACE inhibitor or ARB *vs* β blocker/diuretic (n=3)	4·8–6·1	697 (7%)/10 666	1001 (8%)/11 815	0·80 (0·73–0·88)	<0·001
CCB *vs* β blocker/ diuretic (n=4)	3·5–4·9	1005 (6%)/17 235	1318 (7%)/18 294	0·84 (0·78–0·91)	<0·001
ACE inhibitor or ARB *vs* placebo (n=2)	3·5–5·0	265 (3%)/8448	357 (4%)/8448	0·74 (0·64–0·87)	0·0002
ARB *vs* CCB (n=1)	4·2	690 (13%)/5267	845 (16%)/5152	0·77 (0·69–0·86)	<0·0001

Data are listed according to treatment regimen (n=number of studies). Combination regimens are diuretic-based, with or without β blockers. ARB=angiotensin-receptor blocker. CCB=calcium-channel blocker.

Table 1: **Incidence of new onset diabetes in various studies[40]**

Two additional facts were recorded: first, the commonly used β blocker, atenolol, provided no cardioprotection;[38] second, diuretic-based regimens with or without β blocker provoked more new cases of diabetes than comparator regimens (table 1).[39,40] Overall, these studies question the wisdom of initial therapy with a β blocker, especially in combination with a high dose of diuretic.

The prevailing opinion has been that the protective effect of all classes of drugs against cardiovascular mortality is the same with equal degrees of blood-pressure reduction. The absolute benefit is best in elderly patients and when judged by the fall in systolic blood pressure.[41] Will the ASCOT trial[42] of nearly 20 000 patients change attitudes? The trial was stopped prematurely because of the mortality advantage in the calcium-channel-blocker-ACE inhibitor (CCB-ACEi) group (table 2).[42] Are these results likely to upset the hypothesis that equal blood-pressure reduction provides equal benefits, in favour of initial CCB-ACEi therapy? Is the prime place of β blockers and even diuretics, for so long the mainstay of therapy and often the first choice of drug, now threatened?

β blockers have further lost their previously favoured status as the initial therapy for hypertension. Several powerful arguments favour the view that β blockers should be relegated to third-line therapy. The major reason lies with poor performance as the initial drug in the ASCOT trial.[42] Ancillary reasons are: (1) the meta-analysis showing that atenolol was not as favourable in clinical outcome as other therapies and only slightly better than placebo in stroke reduction;[38] (2) the increased risk of new cases of diabetes if blockers were combined with a diuretic compared with the use of ACE inhibitors, angiotensin-receptor blockers (ARBs), or CCBs;[39,40] and (3) the known side-effects including sexual problems, adverse blood-lipid changes, and weight gain.

	Unadjusted hazard ratio (95% CI)	p
Primary endpoint		
Non-fatal myocardial infarction (including silent) and fatal coronary heart disease	0·90 (0·79–1·02)	0·1052
Secondary endpoint		
Non-fatal myocardial infarction (excluding silent) and fatal coronary heart disease	0·87 (0·76–1·00)	0·0458
Total coronary endpoint	0·87 (0·79–0·96)	0·0070
Total cardiovascular events and procedures	0·84 (0·78–0·90)	<0·0001
All-cause mortality	0·89 (0·81–0·99)	0·0247
Cardiovascular mortality	0·76 (0·65–0·90)	0·0010
Fatal and non-fatal stroke	0·77 (0·66–0·89)	0·0003
Fatal and non-fatal heart failure	0·84 (0·66–1·05)	0·1257

Table 2: **Endpoints for amlodipine and perindopril versus atenolol and thiazide (ASCOT trial)[42]**

But are all β blockers equally ineffective? Important reservations must be made. First, the failure of atenolol-based therapy might be caused by the absence of 24-h efficacy when used once a day. Second, other β blockers might give different results. However, a meta-analysis of β blockers as a group showed that the risk of stroke was 16% higher for β blockers than for other drugs, and that by comparison with placebo or no therapy, β blockers reduced stroke by about half of that predicted from previous studies.[43] More modern β blockers such as carvedilol and nebivolol could be safer than others, with less glucose intolerance, but few major outcome studies in hypertension have investigated this possibility. Carvedilol was better than metoprolol in maintaining glycaemic control as second-line therapy in individuals with hypertension and diabetes who were already receiving an ACE inhibitor or ARB. This difference was associated with a reduction in microalbuminuria only in the carvedilol group.[44] Third, was the diuretic dose used in the trials too high, and thus could be as much to blame as the β blocker? Currently available data do not provide easy answers.

Additionally, does increased serum uric acid, associated with diuretic therapy, cause or indicate cardiovascular harm, or is it a beneficial side-effect of diuretic therapy as an indication of increased antioxidant capacity? In young Japanese men with normotension and an initial blood pressure of 123/70 mm Hg, every rise of 10 mg/L (0·06 mmol/L) uric acid accompanied an increase of mean blood pressure of 27·5/15·2 mm Hg over 5 years.[45] In three other studies, hyperuricaemia predicted the development of hypertension.[46] In a fourth study, increasing serum amounts of uric acid predicted increased target organ damage.[47] Mild hyperuricaemia in

	Compelling indications	Possible indications
α blockers	Benign prostatic hypertrophy	..
ACE inhibitors	Heart failure	Chronic renal disease
	Left-ventricular dysfunction postmyocardial infarction	Type 2 diabetic nephropathy
	Coronary heart disease	Proteinuric renal disease
	Type 1 diabetic nephropathy	
	Secondary stroke prevention (with diuretic)	
ARBs	ACE-inhibitor intolerance	Left-ventricular dysfunction postmyocardial infarction
	Hypertension	Intolerance of other antihypertensive drugs
	Heart failure	Proteinuric renal disease, chronic renal disease
	Post-myocardial infarction	Heart failure
	Type 2 diabetic nephropathy	
	Hypertension with left-ventricular hypertrophy	
β blockers	Myocardial infarction, angina, heart failure	..
CCBs (dihydropyridine)	Elderly patients, angina, isolated systolic hypertension	Black patients
CCBs (rate-limiting)	Angina	Elderly patients
Thiazides or thiazide-line diuretics	Elderly patients, isolated systolic hypertension, heart failure, secondary stroke prevention (with ACE inhibitor)	..

Table 3: **Specific indications for various classes of antihypertensive drugs[32]**

rats promotes preglomerular vascular disease, interstitial fibrosis, salt sensitivity, and hypertension.[46] Conversely and theoretically, diuretic-induced serum urate rise is postulated to be beneficial as a free-radical scavenger.[48] In general, however, increased concentrations of uric acid in individuals with cardiovascular disease are associated with worse outcomes[46] and more serious disease than those with healthy amounts.[47]

Opinion

High concentrations of serum urate imply several disadvantages that outweigh the slight antioxidant benefit that they might confer. Measures to reduce high urate concentrations include the reduction or elimination of the diuretic dose, or the use of losartan as an antihypertensive drug because it lessens the diuretic-induced rise in urate compared with a β blocker.[49] In individuals with hypertension who have gout, uricosurics are often given.

Therapy for specific hypertension-related complications

Do specific drug classes provide varying degrees of protection against individual cardiovascular mortalities? Any conclusions can only be based on scarce data, since few randomised controlled trials have compared different classes of drugs in which equal reductions of blood pressure were observed.

For coronary heart disease, most data show a comparable degree of protection from therapy based on diuretics with or without β blockers, ACE-inhibitors, and CCBs.[4] However, β-blocker-based therapy is not better than placebo.[38] Moreover, ARB-based therapy did not reduce the incidence of myocardial infarction as much as placebo, β blockers, CCBs, or ACE-inhibitors.[50] These interpretations of the data have been strongly contested[51–53] and, in the case of VALUE,[54] could be related to the improved blood-pressure reduction by the comparator. These findings should not be construed as evidence showing that ARBs increases the incidence of myocardial infarction. Rather, they raise the need for more ARB-based trials focused on the incidence of the disorder.

For stroke, a meta-analysis of 103 793 individuals found that dihydropyridine CCBs significantly reduced stroke by 10% compared with other therapies.[55] Only the VALUE trial[54] directly compared a CCB with an ARB, in which the CCB had an early advantage with improved blood-pressure reduction by 4·0/2·1 mm Hg in the first few months. For patients with left-ventricular hypertrophy, ARB (losartan) plus diuretic-based therapy reduced stroke more than atenolol plus diuretic.[49]

For prevention of progression of renal disease, most data are derived from patients with diabetic nephropathy. Among them, most trials for type 1 diabetics use ACE-inhibitor-based therapy whereas most for type 2 diabetes use ARB-based therapy. By strict evidence-based criteria, ACE-inhibitors should be used in type 1 and ARBs in type 2 diabetes. The systematic review by Strippoli and colleagues[56] concluded that ACE-inhibitors and ARBs have equivalent effects on renal outcomes, whereas only ACE-inhibitors have been shown to prevent death. However, for death reduction, this meta-analysis relied heavily on a major study in which diabetic nephropathy was an exclusion criterion, so that by definition this study should have been excluded; furthermore, only 31% had microalbuminuria.[57] In reality, the relative effects of ACE-inhibitors and ARBs on survival are unknown because of the absence of direct comparative trials.

We address two controversies in this section. First, are there additive effects of maximum doses of ACE-inhibitors and ARBs? The combination of an ACE-inhibitor with an ARB provides a somewhat greater reduction in proteinuria but little additive effect on blood pressure.[58] Outcome data are not adequate to assess any survival benefit from the combination. Most currently available trials have combined submaximum doses of ACE-inhibitors and ARBs, thereby skirting the issue of

truly additive benefits. Second, with equal reductions in blood pressure, do different classes of drugs provide additional protection against heart attack, stroke, heart failure, or progression of renal damage?

Opinion

We have slightly different views. NMK concludes that recommendations for certain drugs to be used for certain compelling indications (table 3)[32] seem appropriate for clinical decision making. However, practitioners should realise that head-to-head comparisons in any cardiovascular-renal disease have been inadequate in recording these special benefits. Moreover, many patients carry several compelling indications and the best advice is to reduce the blood pressure to the appropriate goal with whatever is needed while avoiding adverse effects. LHO concludes that there are enough trial data to make recommendations according to the end organ that needs to be most protected. For example, the ACE-inhibitors perindopril and ramipril gave protection from future myocardial infarction, albeit with some blood-pressure reduction in both trials;[57,59] CCBs are marginally better than other treatments to prevent stroke; ACE-inhibitors and ARBs offer improved renoprotection and seem to protect from new cases of diabetes (table 1); finally, β-blocker-diuretic treatment combinations should be avoided whenever the risk of future diabetes is present.

Identifiable causes of hypertension

More identifiable (secondary) instances of hypertension will be seen because their incidence is rising and their diagnosis has now become easier than before. The rising incidence of many causes is for several reasons. Chronic renal disease, probably the most common of identifiable causes, is increasing because more obesity-induced diabetes leads to nephropathy and because individuals with hypertension or diabetes are surviving long enough to develop progressive glomerulosclerosis. Blood pressure is the strongest determinant of decline in the glomerular filtration rate, which with the presence of albuminuria, are the two earliest markers of progressive renal damage.[60] Renovascular hypertension is more common because of increased lifespans in an atherosclerotic environment. Atherosclerotic renovascular disease is now responsible for 90% or more of proven renovascular hypertension, up from 70% a few decades ago.[61] With increased obesity and thicker necks, obstructive sleep apnoea is more common.[62]

Other causes are now being easily diagnosed, often at an earlier stage. Such causes include primary aldosteronism, wherein plasma renin and aldosterone assays can suggest the diagnosis in patients who still have normokalaemia.[63] Phaeochromocytoma can usually be diagnosed with one plasma metanephrine assay.[64] Cushing's syndrome has been found in as many as 5% of patients with an adrenal mass when abdominal scans, using the best current techniques, are undertaken for other indications.[65]

There are several controversies for this issue. (1) Should all patients with hypertension have screening for albuminuria and glomerular filtration rates for earlier recognition of the threat of progression of renal damage? Is the glomerular filtration rate (calculated from a formula based on serum creatinine) adequate for such an estimation? The low cost and potential benefits of screening make the procedures appropriate additions. (2) Should a screening test for renovascular hypertension be done on all individuals with newly diagnosed hypertension? Screening tests should be done since CT and magnetic resonance angiography have been found to be too insensitive to rule out renovascular stenoses.[66] In most academic centres, renovascular testing is only undertaken if there is reasonable clinical suspicion, such as in a young or resistant individual with hypertension, or especially in an individual with an abdominal bruit. Should so-called fly-by renal angiography be done on all individuals with hypertension having coronary angiography? Not unless clinical evidence indicates renovascular disease.[61] Non-renovascular hypertension will not respond to the stenting of a stenosed renal artery. (3) Can obstructive sleep apnoea be diagnosed without an overnight sleep study in a hospital laboratory? The disorder can be strongly suspected in an obese patient with a thick neck who snores at night. (4) What is the best way to assess adrenal adenomas for malignant disease and functionality? The attenuation value obtained by non-contrast CT of the adrenals can be used.[67]

Opinion

Although the incidence of identifiable types of hypertension is increasing, most patients do not need specific screening tests for their recognition unless initial routine assessment suggests their presence. The initial diagnosis should include a careful history, physical examination including waist and neck measurements, and the following laboratory procedures: including urine analysis with albumin-creatinine ratio, haematocrit, serum electrolytes and creatinine with a calculated glomerular filtration rate, fasting glucose and lipogram, and an electrocardiogram (ECG). Measurement of serum uric acid could be a useful precaution if diuretic therapy is selected.

Conflict of interest statement

N M Kaplan has received travel grants and honoraria for speaking at meetings sponsored by Astra-Zeneca, Boehringer-Ingelheim, Merck, Novartis, Pfizer, and Servier. L H Opie has received honoraria and travel grants for speaking at meetings sponsored by Astra-Zeneca, Bayer, Novartis, Pfizer, and Servier; he declares that he has no conflict of interest with respect to this article.

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