HYPERTENSION

Matching the right drug to the right patient in essential hypertension

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In most hospitals, it is cardiologists to whom patients with difficult hypertension are referred. Although these patients may appear a distraction from the sicker patients in cardiac clinics, cardiologists will recognise hypertension as the most common cause of strokes, the most common reversible cause of cardiac failure, and more important than hypercholesterolaemia as a preventable cause of ischaemic heart disease in diabetes.[1] The purpose of this review is to let cardiologists reap some of the fruits of the last two years in the hypertension world, where we now have more answers than questions about the objectives of treatment and how to achieve these, and (with a little didactic licence) we can relate treatment choices to a logical understanding of hypertension itself.

Absolute versus relative risks of hypertension: indications for treatment

Paradoxically, one gulf in our knowledge that remains is that separating our extensive knowledge that hypertension is a major risk factor for stroke and ischaemic heart disease, from an understanding of why hypertension causes these conditions. So unimpressive was the evidence for prevention of ischaemic heart disease in early outcome trials of drugs in hypertension that the question became not *why* but *if* hypertension causes ischaemic heart disease. If treating X fails to prevent Y, maybe X is not a cause of Y after all. This argument has now proven flawed, the fallacy being a confusion between the absolute and relative risks of hypertension. This subtle but vital point is illustrated in fig 1. More patients with hypertension succumb to a myocardial infarction than stroke. But this is simply because myocardial infarction is almost twice as common as stroke in the population at large, and it is only the increased risk from hypertension—the slope of the curves in the graph—which is amenable to antihypertensive treatment.[2 3] The distinction between absolute and relative risk, illustrated in fig 1, has also become central to recent guidelines for the treatment of hypertension.[4] Patients' absolute risk—the y axis in fig 1—depends not only on blood pressure but also on their other risk factors (age, sex, lipids, diabetes), and its calculation is used to postpone the need for treatment in the majority of patients with borderline hypertension (< 160/100 mm Hg). The full British Hypertension Society (BHS) criteria are shown in fig 2.[4] As well as the emphasis on absolute risk in treatment decisions, there should be increasing emphasis in older patients on systolic pressure: more doctors would be inclined to treat patients with a blood pressure of 150/95 mm Hg than 150/85 mm Hg, although the latter carries a higher risk.[5]

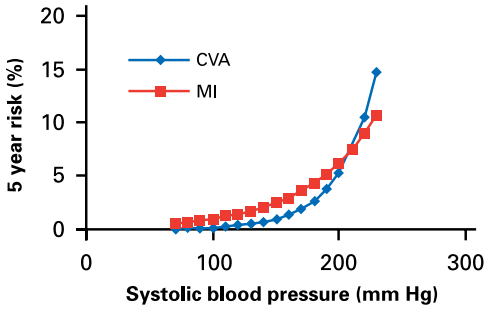

Figure 1. Absolute versus relative risk of myocardial infarction and stroke. Data from MacMahon et al[2] and Collins et al[3] are used to illustrate how myocardial infarction (MI) appears a more common complication of hypertension than stroke (cerebrovascular accident, CVA), because its incidence starts higher in the normal part of the blood pressure distribution. However, stroke has a higher relative risk (plotted as 40% v 25% for each 10 mm Hg increase in systolic blood pressure), and overtakes myocardial infarction as an absolute risk in severe hypertension.

However, the emphasis on absolute rather than relative risk has a down side. If one compares a 35 year old and 75 year old man with a blood pressure 150/95 mm Hg, there is an age paradox.[6] The 75 year old has protection factors to have made it beyond his 70 years, but is at high absolute risk of an event in the next decade. The 35 year old is at low risk of an event within the same period, but at high risk compared to his normotensive peer of failing to reach his 70th birthday. For similar reasons, terms like mild, moderate or severe hypertension are misleading in isolation.[1] The 35 year old has severe hypertension for his age, meaning that he will become the resistant hypertensive of tomorrow, and for this reason should be treated now.

Long term benefits of treatment

The contribution of risk factors other than hypertension itself to absolute risk has long raised the possibility that antihypertensive drugs might vary in their long term efficacy, depending on ancillary actions (for example, desirable or undesired metabolic effects). However, recent outcome trials in hypertensive patients have now shown clearly that there is no difference in the primary composite outcome of stroke and major coronary events between any two classes.[7–11] A rigorous meta-analysis of these, undertaken by the World Health Organization and International Society of Hypertension, confirms this. It also shows that possible differences between classes in cause specific outcomes, of approximately 10%, are minor compared to the difference in outcome between regimens achieving different degrees of blood pressure control.[12] Overall, the conclusion must be that the blood pressure achieved on treatment is more important than the choice of initial therapy. An exception might be the

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Table 1 Compelling and possible indications and contraindications for the major classes of antihypertensive drugs. Reproduced from Ramsay et al[4] with permission of the BMJ Publishing Group

	Indication		Contraindications	
Class of drug	*Compelling*	*Possible*	*Possible*	*Compelling*
α Blockers	Prostatism	Dyslipidaemia	Postural hypotension	Urinary incontinence
ACE inhibitors	Heart failure, left ventricular dysfunction, type 1 diabetic nephropathy	Chronic renal disease*, type 2 diabetic nephropathy	Renal impairment*, peripheral vascular disease†	Pregnancy, renovascular disease
Angiotensin II receptor antagonists	Cough induced by ACE inhibitor‡	Heart failure, intolerance of other antihypertensive drugs	Peripheral vascular disease†	Pregnancy, renovascular disease
β Blockers	Myocardial infarction, angina	Heart failure§	Heart failure§, dyslipidaemia, peripheral vascular disease	Asthma or chronic obstructive pulmonary disease, heart block
Calcium antagonists (dihydropyridine)	Isolated systolic hypertension in elderly patients	Angina, elderly patients	–	–
Calcium antagonists (rate limiting)	Angina	Myocardial infarction	Combination with β blockade	Heart block, heart failure
Thiazides	Elderly patients	–	Dyslipidaemia	Gout

*Angiotensin converting enzyme (ACE) inhibitors may be beneficial in chronic renal failure but should be used with caution. Close supervision and specialist advice are needed when there is established and significant renal impairment.
†Caution with ACE inhibitors and angiotensin II receptor antagonists in peripheral vascular disease because of association with renovascular disease.
‡If ACE inhibitor indicated.
§β Blockers may worsen heart failure, but in specialist hands by be used to treat heart failure.

benefit from the angiotensin converting enzyme (ACE) inhibitor ramipril in the HOPE (heart outcomes prevention evaluation) study.[13] However the mean starting pressure in HOPE, 138/78 mm Hg, was the same as the best blood pressure achieved on treatment in any of the trials in hypertensive patients, and the mechanism of benefit of ACE inhibitors in normotensive patients—including post-myocardial infarction, heart failure or diabetes—may not be relevant to their use in hypertension. This review will therefore concentrate on the optimisation of blood pressure control and how this can be improved by an understanding of hypertension pathogenesis.

Antihypertensive drugs and short term measurement of response

Compared with the three types of drug used in the treatment of angina or heart failure, the range of drugs for hypertension can seem bewildering, and the range of indications and contraindications in the BHS guidelines proves unhelpful in most individual patients (table 1). Although, however, there are eight classes of drugs available—ACE inhibitors, β blockers, calcium channel blockers, diuretics, angiotensin receptor blockers, α blockers, centrally acting drugs, and direct vasodilators—the first four of these are sufficient to account for most current prescribing in hypertension in almost equal measure (if only treatment initiations are counted). There are two coincidences. One is that the first four are also the ones used in angina or heart failure, whereas some of the others would be contraindicated (changing a hypertensive patient from β blockade to α blockade, for example, is quite an effective provocation test for angina). The second is that the names of these four classes start with the first four letters of the alphabet. The felicity of this coincidence is accentuated by the antithesis between the AB and CD pairs, as will become apparent, giving rise to a mnemonic "AB/CD" rule introduced later that forms the basis of our approach to the treatment of hypertension.[14]

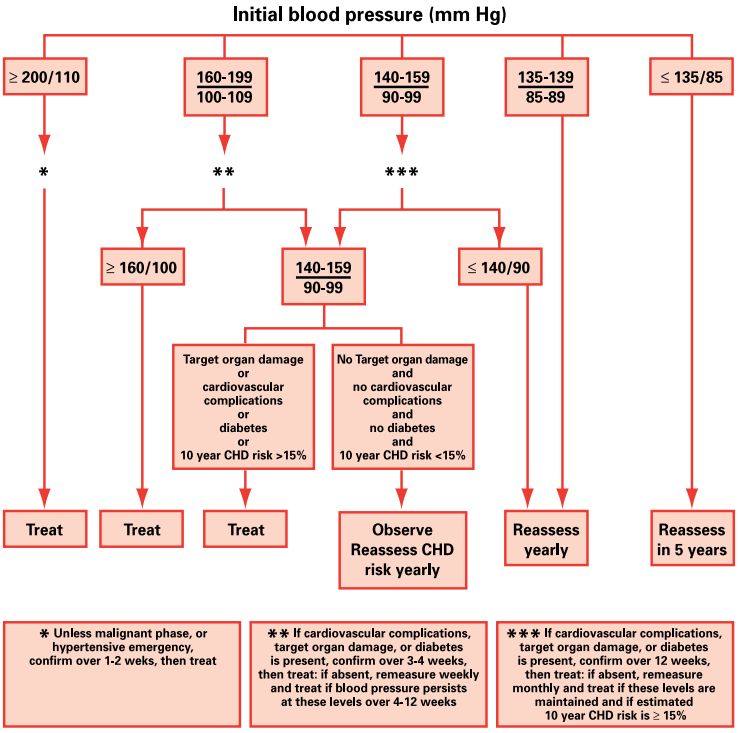

Figure 2. Blood pressure indications for treatment (British Hypertension Society guidelines). Reproduced from Ramsay et al,[4] with permission of BMJ Publishing Group.

If the long term objectives in hypertension treatment are prevention of the cardiovascular complications, the short term objectives measurable in every patient are simply reduction in blood pressure and avoidance of adverse effects. The only room for controversy here concerns the blood pressure target and whether treatment that avoids adverse effects actually improves quality of life in apparently asymptomatic patients. Two large studies—TOMHS (treatment of mild hypertension study) and HOT (hypertension optimal treatment)—do indeed support the latter notion.[15 16] Coupled to the evidence, from one outcome trial, that blood pressure treatment prevents dementia,[17] we have the beginnings of a story that patients compliant with treatment will have improved mental and physical well-being. This story is weaker than the main argument for treatment, but perhaps it can become a useful adjunct for patients for whom prevention of a stroke in future decades seems insufficient incentive to take daily treatment for an asymptomatic condition.

The question of blood pressure targets is probably more important, but one which engenders more heat among protagonists than enlightened interest in the minds of readers. The observational data strongly suggest that the lower the blood pressure the better.[2 3] When one turns to the evidence from individual outcome trials, only analyses in diabetics have successfully shown the value of more rather than less blood pressure reduction, and even these do not come close to justifying the targets recommended by diabetes associations.[10 18–20] The methodological problem is that of dissociating lower blood pressure on treatment from a lower blood pressure before treatment (about whose predictive value there is no argument). The situation is compounded by confusion between systolic and diastolic targets, and the recognition that in older patients there is an *inverse* relation between diastolic pressure and risk.[5] The recommended target is 140/85 mm Hg, with a "minimum audit standard" of 150/90 mm Hg.[4] This duality may sound like first and second class post, but it is a sensible recognition that first class post cannot be delivered in all patients. Although the guidelines recommend that both the systolic and diastolic targets are achieved, in practice doctors will accept success with one of them—most likely the diastolic target. It has therefore been suggested that target setting be unified by dropping the diastolic altogether.[21] Certainly it is important to involve the patients in the process of target setting: they must be told both what their blood pressure is and what it should be, and chances of their remembering are doubled by adhering to a single figure.

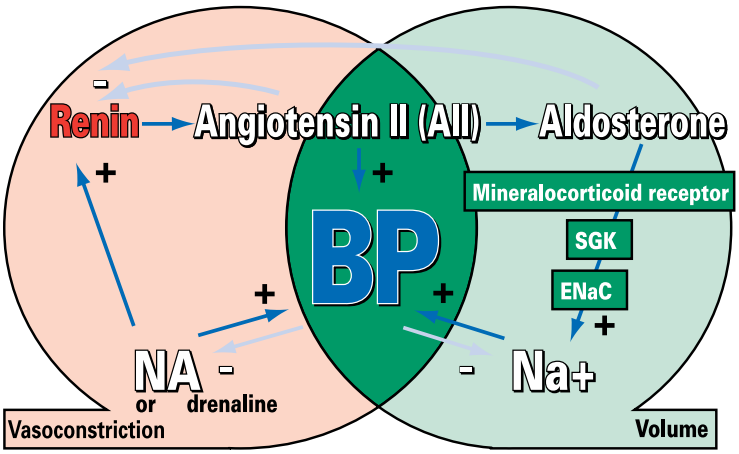

Figure 3. NA or Na in hypertension? The principal initiating factors in hypertension are noradrenaline (NA) released from sympathetic nerves, which causes vasoconstriction, or sodium (Na^+) which increases blood volume. Since blood pressure = peripheral resistance × cardiac output, hypertension cannot occur until vasoconstriction by noradrenaline and its stimulation of renin secretion fails to be offset by pressure natriuresis. Apart from the key players of NA, Na^+, renin and angiotensin, there are a very large number of molecules involved in the synthesis, secretion or response to these, which provide candidate genes to explain inherited susceptibility to hypertension. The figure illustrates just three of these, relevant to the cell signalling of aldosterone. ENaC, epithelial sodium channel; SGK, serum glucocorticoid kinase.

A unitary scheme for pathogenesis of hypertension, and implications for rational choice of treatment

In turning from the objectives to mechanics of antihypertensive treatment, we are now in the fortunate position of having both evidence and a logical basis for what we recommend. In the 1970s and early '80s it was fashionable to propose unitary hypotheses for hypertension. One of those was centred on the renin system, which seemed to be more important in young, white patients and gave way to other systems of blood pressure control in older patients.[22 23] As molecular genetics came of age, it became clear that hypertension is one of the "common complex disorders", and the involvement of multiple genetic variants—probably most in yet unknown genes—has now been confirmed on a genome wide scan.[24] We therefore sought evidence that different patients have a different "best" drug, depending on the genetic basis for their hypertension. The possibility of this had been suggested by previous crossover comparisons.[25–28] Surprisingly, however, when we rotated patients through all four of the main classes, there was a clear pattern that most patients responded well to one or other of the AB and CD pairs mentioned earlier[11]; we have recently repeated this study double blind, incorporating also α blockade and a placebo control.[29] I believe now that, while there is great heterogeneity at the molecular level, this should not blind us to the central part of one or two systems, in which these molecules play a part.

The key lies in one of the fundamental laws of cardiovascular physiology—that blood pressure is the product of cardiac output and peripheral resistance—and this gave rise many years ago to the concept that there are separate volume and vasoconstriction phases or types of hypertension.[30] Figure 3 seeks to satisfy both the lumpers and splitters' approach to a complex disorder like hypertension. Noradrenaline (NA) and salt (Na^+) are better contenders than renin itself for initiating the processes

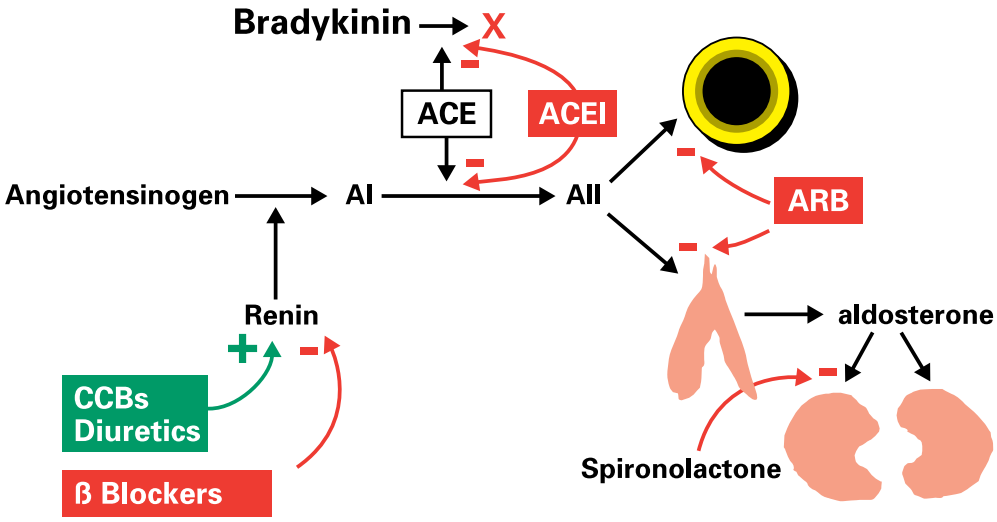

Figure 4. Drugs acting on the renin-angiotensin-aldosterone system. Drugs which suppress the system are shown in red, those which activate the system are in green. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCBs, calcium channel blockers.

leading to hypertension, but it is the renin system which should be arraigned when explaining either the raised peripheral resistance in established hypertension or how this responds to the different drug treatments (fig 4). A large number of molecular candidates up and downstream of renin will probably be found to harbour genetic variants which illuminate understanding of hypertension in individual patients; but measurement of plasma renin is likely to remain the best single guide to the type of hypertension and choice of treatment.[22]

Some attempt is required to overcome the paradox that we *can* control blood pressure when following a rational protocol,[10 20] but in everyday practice fail to achieve this in 90% of patients.[31] Diabetologists have successfully separated diabetes in doctors' minds into types 1 and 2, with clear therapeutic implications, without having a clear idea about the cause of either other than the relative lack or excess, respectively, of insulin. It would be wrong to press the analogy with hypertension too far. Nevertheless, a similar notional division of hypertension into types 1 and 2 may help promote more rational and effective drug treatment. Type 1 would be the vasoconstrictor, high renin type of hypertension seen in younger white patients; type 2 would be the volume dependent, low renin hypertension seen in African Caribbean and older white patients. Taking figs 3 and 4 together, it is apparent that type 1 (high renin) hypertension should be treated with a renin suppressing drug, A or B (ACE inhibitor or β blocker), whereas type 2 (low renin) hypertension should be treated with C or D (calcium channel blocker or diuretic).

It also follows that salt is not, in whites, a major influence early in hypertension, and dietary advice should focus on reducing fat, and increasing fruit and fibre intake.[32] In the early stages of hypertension development—recognisable clinically as a phase of labile hypertension, where the negative feedback loops in fig 3 are still operative—sole treatment with a β blocker is the most effective. It is likely that at this stage increased cardiac output contributes to the raised blood pressure, and β blockade blocks the action of noradrenaline both upon the heart and upon renin release.[33] Once hypertension is sustained, the role of renin becomes predominant and ACE inhibitors can be the most effective treatment. It is interesting to speculate whether this transition from what might be considered a high flow to high pressure system has any useful analogy with that recognised on the right side of the circulation in patients with congenital cardiac left to right shunts. At the least, such patients demonstrate the long period of time over which structural changes can develop in the vasculature, and support the view that even young patients with established hypertension already have an end stage disease. Two years after using the AB/CD strategy to lower blood pressure in 37 patients (mean age 41 years) to 125/75 mm Hg, we stopped treatment. Blood pressure promptly returned to pretreatment values, and estimation of arterial stiffness showed this had remained high despite the "prolonged" period of normotension.[34]

Volume dependent (low renin) hypertension may be primary, typically in African Caribbean patients, in Conn's syndrome,[35] and in a rare group of monogenic syndromes caused by activating mutations in a Na^+ transporter[36] or the aldosterone pathway.[37–39] Indeed the latter patients illustrate well the principle of fitting the treatment to the cause of hypertension, with spironolactone or amiloride, respectively, being particularly effective in patients with increased stimulation of the mineralocorticoid receptor or epithelial sodium channel (ENaC, fig 3), respectively. However, most white patients do not have primarily volume dependent hypertension, and the transition to this may be secondary to renal or renovascular consequences of the hypertension. These patients may need a combination of a calcium channel blocker or diuretic (C or D), which is the preferred initial treatment in low renin hypertensives, with a renin suppressing drug—ACE inhibitor or β blocker (A or B). In effect, C or

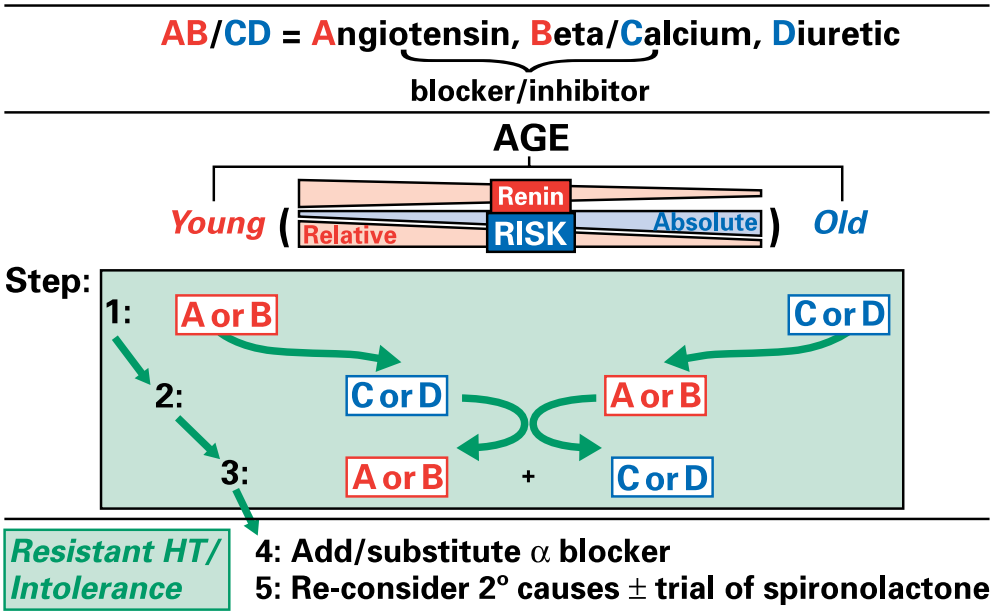

Figure 5. AB/CD schema for optimisation of antihypertensive treatment. In choosing initial treatment—step 1—age in a white population is used as a surrogate for plasma renin, which falls with age. The typical younger patient (aged < 55 years) responds better to ACE inhibition or β blockade, whereas in the older patient (aged > 55 years) calcium channel blockade or diuretic is the preferred starting treatment; angiotensin receptor blockade can substitute for ACE inhibition in intolerant patients. Because the response of patients to the two drugs within each pair is well correlated, there is usually no point in switching an unresponsive patient to the other of the pair (for example, A to B); therefore step 2 in such a patient is to switch to one of the other pair. If the blood pressure is still above target, step 3 is to combine one drug from each pair.

D not only lowers the blood pressure but converts a previously low renin patient into a higher renin patient who can respond to the addition of A or B. Given that the older patients, in whom C or D are the initial drugs of choice, are also those at higher absolute risk of complications, combination therapy should increasingly be the norm. Diabetics in particular require more drugs than other patients, and may not achieve the stiff targets set for them.[18 40] It is time therefore to cease the arguments over whether ACE inhibitors or calcium channel blockers are preferable among the newer classes, and instead ensure that any patient with microalbuminuria is receiving both. Among all patients, it is also time to encourage greater use of combination formulations, in recognition of patients' desire to minimise their tablet intake.

The AB/CD rule

At this point the recommendations and arguments can be summarised in the form of an AB/CD rule (fig 5). This arises not only from the small rotation studies, but also from previous observations on the influence of age upon drug response in parallel groups studies.[23 41–43] The somewhat arbitrary age definitions are based on the two studies which initially suggested the rule: a rotation through all four drug classes in patients aged < 50 years,[14] and a randomised comparison of C and D, with addition of A or B, in patients aged > 55 years.[10] The schema shown in fig 5 does not advise on dose; clinical judgement is still required to assess whether a small response to the initial dose is mainly placebo response or will increase with dose. The advice of a pharmacologist, whenever there is doubt about efficacy or tolerability, is to try doubling the dose—true drug effects follow a dose-response curve.

The schema also skirts the issue of whom to treat. Current British guidelines recommend treatment in patients with a blood pressure > 160/100 mm Hg, or > 140/90 mm Hg if there is >2% annual risk of stroke or coronary heart disease (fig 2). As discussed already, systolic pressure alone may be preferable; more doctors would be inclined to treat a patient with a blood pressure of 150/95 mm Hg than 150/85 mm Hg, although the latter carries a higher risk.[5] As the schema also suggests, the younger hypertensive patient is likely to have high renin hypertension and the renin may itself be a risk factor for coronary heart disease.

Investigation and treatment of resistant hypertension: importance of aldosterone

One term which the AB/CD rule helps to define is resistant hypertension; this is a blood pressure above target despite a combination of [A or B] + [C or D]. This is helpful to recognise as a discrete entity because resistance to a conventional therapeutic attack on the volume and vasoconstriction elements of hypertension implies an extra, or unusual, stimulus to one of these. Alcohol is the most common curable cause of resistant hypertension. Reflex sympathetic activation requiring α blockade is another, and may be suggested if slightly raised noradrenaline excretion is found during the

tests to exclude phaeochromocytoma as a secondary causes of hypertension.[44] In the presence of impaired renal function, bilateral renal artery stenosis should be sought by magnetic resonance imaging. Of most interest now is hyperaldosteronism. There is no doubt that primary hyperaldosteronism, or Conn's syndrome, is underdiagnosed.[45 46] In a survey of 800 unselected patients in primary care, we have found almost 10% of patients to have raised aldosterone to renin ratios and blood pressure more responsive to spironolactone than other drugs. This prevalence is comparable with findings from hospital based studies, and the outstanding finding is that in many cases the plasma potassium (K^+) concentration is normal, even > 4.0 mmol/l. Only a handful of these patients have adrenal adenomas.

In such a cross-sectional study, it is not possible to know whether hyperaldosteronism in the absence of an adenoma is the primary cause of the hypertension, or a tertiary development after long standing hyper-reninaemia. From a therapeutic standpoint, this is academic. Although a single outpatient sample is sufficient for measurement of renin and aldosterone, the infrequency of adenomas suggests that the response to spironolactone can be undertaken first as a therapeutic test. At a dose of 1 mg/kg daily (to the nearest 25 mg), gynaecomastia is rare, and should be avoided altogether with the advent of more specific aldosterone antagonists.

What about the really resistant patient, the one uncontrolled on four or five drugs? Assuming that none of the above strategies has worked, the ultimate "weapon" is minoxidil. This is the most powerful vasodilator, almost guaranteed to normalise blood pressure provided patients can tolerate β blockade and high doses of a loop diuretic. However, side effects such as hirsutism and coarsening of facial features render this the treatment of last resort, though patients who have endured the adverse effects of other drugs can be surprisingly resilient. One promising alternative is the combination of second generation angiotensin and aldosterone receptor blockade; this appears the most effective way of targeting the whole of the renin system, blocking both the vasoconstrictor and volume drivers of hypertension.

Emergency reduction of blood pressure

This article has concentrated on the hypertensive outpatient, but there are rare occasions when emergency treatment for high blood pressure is indicated. It is important to differentiate these indications from the similarly rare occurrence of accelerated phase hypertension; the latter is almost a contraindication to emergency reduction of blood pressure because of the loss of cerebral autoregulation and consequent risk of cerebral infarction. The three indications for emergency reduction are hypertensive encephalopathy (of which eclampsia is the most common cause),

Key points

- Community surveys show that less than 10% of patients have a blood pressure at target
- Recent outcome trials show that achieved blood pressure is much more important than choice of initial drug in preventing stroke and myocardial infarction. Therefore strategies for optimising blood pressure control in the individual patient are paramount
- In more than 90% of patients, the cause of hypertension remains unknown
- Primary hyperaldosteronism (Conn's syndrome) accounts for at least 5% of hypertension, and usually presents with normal plasma electrolytes
- Numerous molecular variants are being found which contribute a small amount to the development of hypertension. Patient response to different drugs may depend in part on which of these is inherited
- The main determinant of response pattern is the patient's age. This probably reflects the dominant role of the renin system in blood pressure regulation
- Younger patients have relatively high renin concentrations and respond well to drugs which suppress the renin system—ACE inhibitors, angiotensin receptor blockers (A), and β blockers (B)
- Older patients have low renin concentration, and respond well to drugs which do not suppress renin—calcium channel blockers (C), and diuretics (D). These drugs actually cause reflex activation of the renin system, and therefore make patients more sensitive to A or B
- Target blood pressure is 140/85 mm Hg, or 135/80 mm Hg in diabetics. Less than 50% of patients are likely to reach these targets on one drug
- The best combinations have complementary actions on the renin system—that is, one of [A or B] + one of [C or D]
- Resistant hypertension is a blood pressure > 140/85 mm Hg despite treatment on such a combination. Such patients should be screened for secondary causes. Treatment options include addition of an α blocker, or a trial of spironolactone ± an angiotensin blocker.
- Rarely, patients require treatment with minoxidil, the most powerful vasodilator available

left ventricular failure, and dissecting aneurysm. Parenteral treatment with nitroprusside for a maximum of 2–3 days is advisable for the first two conditions, whereas more prolonged treatment with parenteral nitrate and labetalol are preferable for the latter; this combination is also useful for any other patients requiring excellent blood pressure control and parenteral treatment. Accelerated phase hypertension is best treated with low dose oral β blockade. In none of these circumstances is short acting nifedipine advisable, but long acting calcium channel blockade may be started as cover for parenteral treatment that can be down titrated as the oral treatment starts to be effective.

Conclusion

Hypertension describes the upper end of the blood pressure distribution, in which there is a high relative risk of cardiovascular disease. It is a complex disorder in that a variety of genetic and environmental factors, many as yet unknown, determine an individual's point in the blood pressure distribution. However, the main physiological and biochemical systems controlling blood pressure are well understood, as are their responses to the drugs used for treating hypertension. Hypertension occurs when excessive vasoconstriction and/or volume are not compensated, respectively, by adequate pressure natriuresis or suppression of the renin-angiotensin-aldosterone system. The AB/CD rule for treatment minimises the steps required in individual patients to achieve these compensatory adjustments. Possible differences between drug classes in prevention of stroke or coronary heart disease are minor compared to the importance of blood pressure control. This is ideally assessed by 24 hour ambulatory monitoring of blood pressure and its impact on left ventricular mass.

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