ABSTRACT – There is a greater choice of drug classes for hypertension than most other diseases, increasing paradoxically the difficulty of finding the right drug for individual patients. Systematic drug rotation studies have shown that the rank order of response to different drugs varies substantially among patients. However, two broad patterns of response emerge, named after the initials of the major drug classes. The AB pattern is seen in Type 1 (high-renin) hypertensives. These are younger Caucasians who respond best to angiotensin-converting enzyme (ACE) inhibitors, angiotensin blockers and β-blockers. The CD pattern is seen in Type 2 (low-renin) patients. These are Afro-Caribbeans and older Caucasians, who respond best to calcium blockers and diuretics. This relative homogeneity of phenotype at each age group contrasts with a large heterogeneity of genotype on recent genome-wide scans, and suggests that most hypertension is due to interaction among multiple minor genetic variants. Genotype is unlikely therefore to be useful in selecting treatment for most patients. The exception is patients who have the atypical phenotype for their age, illustrated by the rare Na⁺ dependent monogenic syndromes of the young.

KEY WORDS: aldosterone, cross-over study, hypertension, pharmacogenetics, spironolactone

Hypertension is a major risk factor for cardiovascular events and stroke. There is a greater genuine choice of drugs available for hypertension than for any other indication, but the majority of patients with hypertension have blood pressures far above recommended targets. This failure is due partly to inappropriate choice of drugs and partly to insufficient use of combinations. Additionally, the trend in recent guidelines to emphasise absolute cardiovascular risk as a criterion for initiating treatment has the undesired effect of delaying treatment for a critical period in the younger patient at high relative risk of becoming treatment resistant when older.

We have been interested in two complementary strategies for finding the best treatment for patients:

1. An empirical approach, aiming to find the best treatment by systematic rotation.
2. A rational approach in which it might eventually be possible to predict response from a knowledge of genetic variants.

The two approaches are complementary because patients’ best drug on rotation may give a clue to the pathway by which variants are most likely to be found. Paradoxically, the rotation strategy showed surprising uniformity in the pattern of drug responses, falling into two main types determined more by age than by genotype. This has allowed the development of a didactic age-related AB/CD rule, based on the serendipitous coincidence of these letters with the initials of the main drug classes:

- (A) angiotensin-converting enzyme (ACE) inhibitors
- (B) beta-blockers
- (C) calcium-channel blockers (CCBs)
- (D) diuretics.

However, we believe that age is a surrogate for renin status, and that the limited heterogeneity of the pharmacological phenotype is consistent with extensive heterogeneity of genotype among the many genes that influence secretion or response within the renin-angiotensin-aldosterone pathway. Thus, we predict that patients presenting young may have variants which increase sympathetic nervous stimulation of renin, whereas older patients are more likely to have suppressed renin due to activation of aldosterone secretion or response.

Until recently, it was possible to relate blood pressure control to the status of surrogate end-point whose correlation with outcome was not established. Recent outcome trials, however, have shown that blood pressure control is paramount in determining outcome, with differences between drugs of secondary importance to differences in blood pressure control. The evidence for these statements will be reviewed; these, in turn, justify the search for strategies which optimise blood pressure control as those most likely to optimise outcome in hypertension. The different drug classes appear to show small differences in influence upon individual outcomes, such
as stroke, coronary heart disease and heart failure. We shall point out, however, that available evidence argues for routine combination of drugs in order to maximise benefit rather than selecting one class as preferable to any other.

Drug therapies for hypertension

Several different classes of drug are available for the treatment of hypertension (Table 1). The most important goal of therapy is the achievement of adequate blood pressure reduction. However, it is becoming apparent that drugs may have differing effects on the pulse wave and endothelial function, as well as differing metabolic effects. Some of these may explain cause-specific differences in long-term outcome such as the incidence of heart failure, stroke or new diabetes.

Comparison of outcomes using different classes of drugs

A prospective meta-analysis has compared the effects of CCBs versus beta-blockers or diuretics in the treatment of hypertension on the incidence of stroke alone, non-fatal myocardial infarction (MI) or coronary heart disease (CHD) death, and stroke, MI or cardiovascular death. Using data mainly from the INSIGHT\(^1\), STOP 2\(^2\) and NORDIL\(^3\) studies (see end of text for explanation of studies), a small but significant reduction was found in the incidence of stroke with a CCB compared with a beta-blocker or diuretic (relative risk (RR) 0.86, 95% confidence interval (CI) 0.76–0.97). There was a trend towards a reduction in non-fatal MI or CHD death with a beta-blocker or diuretic compared with a CCB which just failed to reach significance (RR 1.12, 95%CI 1.00–1.26). Combining cerebro- and cardiovascular end-points showed no overall difference between CCBs and beta blockers/diuretics (RR 1.00, 95%CI 0.93–1.09).

The same authors analysed anti hypertensive therapy using ACE inhibitors with beta-blockers or diuretics\(^4\) and found no difference in the incidence of stroke (RR 1.05, 95%CI 0.92–1.20), non-fatal MI or CHD death (RR 0.99, 95%CI 0.87–1.13), or the composite of stroke, MI or cardiovascular death (RR 1.02, 95%CI 0.94–1.11). This meta-analysis used data from the STOP 2, UKPDS\(^5\) and CAPP\(^6\) studies. The LIFE study has subsequently reported a 13% overall advantage for the combination of the angiotensin blocker and diuretic compared with atenolol and diuretic (RR 1.00, 95%CI 0.93–1.09).

Importance of adequate treatment

The optimal targets for blood pressure reduction are not yet known. National guidelines are updated at intervals as further information becomes available. At present, the British Hypertension Society guidelines quote a target blood pressure of below 140/85 mmHg for most patients, 5 mmHg lower in patients with diabetes. In the HOT study\(^12\), the lowest incidence of cardiovascular events occurred at mean achieved diastolic and systolic blood pressures of 82.6 mmHg and 138.5 mmHg, respectively.

In a retrospective meta-analysis of nine randomised trials comparing treatments in 62,605 hypertensive patients, Staessen et al\(^14\) correlated reported differences in outcome between arms of the trials with differences in blood pressure control. This is a challenging analysis because of the difficulty of standardising what is meant by ‘achieved’ blood pressure at different times in different trials. The results appeared to show that differences between treatments were explicable entirely by differences in blood pressure control.

Systolic or diastolic blood pressure

Which of these is the better predictor of risk? The traditional view was that diastolic blood pressure is the more important measure. However, analysis of data from population studies, in

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**Table 1. Drugs used for the treatment of hypertension.**

<table>
<thead>
<tr>
<th>Main drug classes</th>
<th>Angiotensin-converting enzyme inhibitors</th>
<th>Angiotensin receptor antagonists</th>
<th>Beta-blockers</th>
<th>Calcium-channel blockers</th>
<th>Diuretics</th>
<th>Alpha-blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less commonly used</td>
<td>Centrally acting drugs</td>
<td></td>
<td>Vasodilators</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Systolic or diastolic blood pressure**

Which of these is the better predictor of risk? The traditional view was that diastolic blood pressure is the more important measure. However, analysis of data from population studies, in
particular the Framingham study\textsuperscript{15}, demonstrated that systolic pressure is a better predictor of outcome at least in the over-55 years age group. The difference between systolic and diastolic pressure (ie pulse pressure) is also an important predictor of cardiovascular risk in this group of patients\textsuperscript{16}. Both 24-hour mean blood pressure and 24-hour pulse pressure correlate with risk of stroke and coronary artery disease\textsuperscript{17}, but the former seems to be the more important in predicting stroke while pulse pressure has a greater influence on cardiac events. There was a similar finding in the Medical Research Council Mild Hypertension Trial\textsuperscript{18} in which diastolic and systolic pressure were measured rather than mean and pulse pressure, respectively.

In the INSIGHT study, one of the few double-blind outcome trials, an accurate comparison of the effects of the long-acting CCB nifedipine (gastrointestinal transit system (GITS)) and diuretic combination co-amiloizde on blood pressure found greater reductions in diastolic and systolic blood pressure, respectively, with these drugs. The differences were of the order of 1 mmHg, which is highly significant in several thousand patients, and is one possible explanation for the small cause-specific benefits of these two classes in the meta-analysis discussed earlier\textsuperscript{1}.

**Genetics of hypertension**

In the vast majority of cases, hypertension is caused by a combination of genetic and environmental influences. Recent genome-wide scans have failed to find many regions (‘loci’) where affected siblings share the same alleles of a polymorphic microsatellite marker more frequently than the 25% incidence expected by chance alone. This suggests that the genetic basis of hypertension is highly heterogeneous, with few genes contributing more than a few percent of blood pressure variance. There are two possible models for this heterogeneity:

1. **High frequency, low penetrance** in which the same multiple genes contribute a few percent to most patients’ hypertension.

2. **Low frequency, high penetrance** in which most patients (families) have hypertension caused by only two to three genetic variants, their identity differing among families.

It is presently unclear which is the correct model for the heterogeneity. The latter is the more attractive scientifically in that the genes, when discovered, may teach us something substantial about pathogenetic mechanisms – but neither model is likely to be of use for predicting the best treatment for an individual patient from individual genetic variants. This is unlikely to change until or unless most of the variants involved in hypertension are known and there is a cheap method for simultaneous analysis of hundreds of genotypes.

The evidence for the idea that knowing the cause of hypertension in an individual patient will predict their best drug is illustrated in Table 2. In both the rare monogenic disorders and the better known secondary causes of hypertension there is a preferred drug which lowers blood pressure much more than the approximately 10% average achieved by random choice of single drugs in essential hypertension.

One of the monogenic syndromes in Table 2, Gordon’s syndrome (pseudohypoaldosteronism type II), illustrates how a study of drug response can help elucidate a new mechanism. Patients with this syndrome have the phenotype of early onset low-renin hypertension and elevated $K^+$ and $Cl^-$ levels, with reversal of all abnormalities by thiazides. This suggested a genetic variant in the thiazide sensitive $Na^+/Cl^-$ co-transport (NCCT) channel. However, linkage studies showed that the mutation could not be in the gene for NCCT and led recently to a novel ‘with no lysine (K)’ (WNK) family of kinases\textsuperscript{19}. The substrate for these kinases remains to be elucidated, but localisation of WNK4 to the tight junction of the cortical collecting duct cells, rather than being co-localised with NCCT, has suggested that $Cl^-$ rather than $Na^+$ drives the hypertension and that $Cl^-$ transport is paracellular.

**Rotation studies**

The contribution from individual genetic variants is much smaller in essential hypertension than in the monogenic syndromes, and it has been more difficult to demonstrate clear associations between common polymorphisms and drug response\textsuperscript{20}. In order to determine whether there is evidence for similar heterogeneity of drug response in essential hypertension

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**Table 2. Monogenic disorders causing hypertension and other secondary causes of hypertension.**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Cause</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monogenic disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liddle’s</td>
<td>ENaC (β or γ subunit)</td>
<td>Amiloride</td>
</tr>
<tr>
<td>GRA</td>
<td>Aldosterone synthase chimera</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Apparent mineralocorticoid excess</td>
<td>Liquorice, $11β$HSD mutation</td>
<td>Spironolactone</td>
</tr>
<tr>
<td>Gordon’s</td>
<td>WNK1 or WNK4</td>
<td>Thiazide</td>
</tr>
<tr>
<td><strong>Mainly acquired syndromes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conn’s</td>
<td>Adrenal adenoma</td>
<td>Spironolactone</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Chromaffin tumour</td>
<td>Phenoxybenzamine</td>
</tr>
<tr>
<td>Renal artery stenosis</td>
<td>Fibromuscular hyperplasia</td>
<td>ACE inhibitor or angiotensin receptor antagonist</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; ENaC = epithelial sodium channel; GRA = glucocorticoid remediable aldosteronism; HSD = hydroxysteroid dehydrogenase; WNK = ‘with no lysine (K)’ (family of kinases).
as among the different monogenic syndromes – suggesting that essential hypertension might be a basket of semidiscrete syndromes each with an optimal treatment – we have conducted the following series of studies in which patients rotate through a predetermined set of antihypertensive agents of different classes:

1. An open-label rotation through the four major classes, with a month’s washout between each drug.21
2. A double-blind comparison of the four major classes with placebo, also incorporating -adrenergic blockade as one limb.
3. Home blood pressure monitoring to allow rapid rotation through all possible permutations of combination as well as single treatments.

The studies have indeed demonstrated true variability such that a drug chosen at random is unlikely to be a patient’s most effective drug. However, patients and their responses to drugs clearly fall into two main types:

1. Higher-renin patients, particularly younger Caucasians, respond better to drugs which suppress the renin system.
2. Lower-renin patients, who are older or Afro-Caribbean, respond better to drugs which cause vasodilatation and natriuresis. This causes reflex activation of renin, so the patients are converted to a higher-renin type patient – in whom it is then logical to add one of the renin suppressing drugs.

The AB/CD rule

This approach is summarised in our AB/CD rule (Fig 1, Table 3) which drew its name from the coincidence noted between these letters and the initials of the main drug classes. The AB/CD rule suggests that the first drug of choice for treating hypertension in younger patients should be an ACE inhibitor (A) or beta-blocker (B), while older patients are likely to respond better to a CCB (C) or diuretic (D). If this is insufficient to control blood pressure, patients should first be switched to one of the other agents (eg from A or B to C or D or vice versa). If single agent therapy still proves insufficient to control the blood pressure to target, A or B should be combined with one of C or D. (One exception to this rule is Black people who tend to have a low renin form of hypertension and should therefore usually be started on either C or D as first-line therapy.)

Our rotation among combinations, still in progress, has also served to emphasise that there are individual exceptions to AB/CD, with angiotensin blocker plus beta-blocker an impressive combination in 6/33 patients.

The rule is not novel, in the sense that an influence of renin status on response to treatment has been demonstrated for diuretics and beta-blockade, and various previous rules have pointed to the logic of combining these types of drugs22,23. It is the correlations in the rotations between the responses to the

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Table 3. The AB/CD rule for the management of hypertension (see Fig 1).

<table>
<thead>
<tr>
<th>Step</th>
<th>Management option</th>
</tr>
</thead>
</table>
| 1    | Patients selected according to age or renin status  
Younger patients (aged <55) |
| 2    | Switch to the alternate pair if systolic blood pressure falls <5 mmHg on step 1 |
| 3    | Combine one each of the two pairs |
| 4 & 5| Suggestions for the treatment of patients not controlled on optimal combinations of two drugs |

Figure 1: The AB/CD rule for optimisation of antihypertensive treatment (see Table 3) (ACEi = angiotensin-converting enzyme inhibitor; HT = hypertension).
ACE inhibitor (A) and the beta blocker (B) and between the responses to the calcium channel blocker (C) and the diuretic (D) which show that the newer drug classes have not substantially increased our success at controlling blood pressure with a single agent (although to have a choice is obviously welcome for patients who are unable to tolerate the other member of the pair).

Demonstration of the correlation between A and B is timely since some doctors may regard the LIFE study as an indictment of all beta-blockers rather than solely of atenolol. An ACE inhibitor or angiotensin blocker can usually be substituted for a beta-blocker without loss of blood pressure control. Pulse wave analysis in our studies suggests a possible reason why beta-blockers may not achieve predicted benefits of blood pressure reduction. The bradycardia allows pulse wave reflection from the arterial tree to occur during the prolonged period of systole. Beta-blockers were found to be the only class of drugs to enhance augmentation of the central aortic pulse wave even when brachial artery pressure falls (Fig 2). In the same study there was a threefold rise in brain natriuretic peptide secretion, a marker of left ventricular strain, which suggests that the augmented systolic pulse wave may not be benign.

**Monotherapy versus combination therapy**

In our first study of young patients (mean age 41) 73% achieved a systolic blood pressure of 140 mmHg or below on their best drug. The subsequent studies in slightly older patients found that almost half of them were still above this target. The objective of these rotation studies was to determine how to find patients’ best initial treatment, but they have also served to emphasise the increasing need to regard combination treatment as the norm. This is likely to be especially true of older patients, in whom there is an additional reason beyond blood pressure control for recommending combination therapy (see below).

There is first the need to consider the patients reaching the bottom section of the AB/CD schema, in whom combination of two drugs is insufficient. The schema permits a standard definition of resistant hypertension as blood pressure not controlled on a combination of one drug from each of the AB and CD pairs. We have been interested in this group both because they comprise a large part of specialist hypertension practice and because, as exceptions to the rule, they might be the patients in whom it is possible to define a phenotype where genetic variants play a greater role.

**Use of spironolactone in resistant hypertension**

Several studies have pointed to the value of spironolactone in patients with poorly controlled hypertension – the response is often dramatic. We have recently completed a study investigating the prevalence of aldosterone-sensitive hypertension in 835 unselected patients with hypertension in primary care. All patients had plasma aldosterone and renin measurements; the effect on blood pressure of spironolactone 50 mg was investigated in all those with an aldosterone/renin ratio above 800 or suppressed plasma renin. Almost 10% of the patients met the prespecified diagnostic criteria for primary hyperaldosteronism (PHA): an aldosterone/renin ratio above 800 and a fall in SBP during spironolactone therapy of at least 20 mmHg.

In addition, the existence of a group we have previously called ‘normal aldosterone spironolactone sensitive hypertension’
(NASSH) was confirmed: that is, those who have previously resistant low-renin hypertension responsive to spironolactone but not to thiazide diuretics, in whom plasma aldosterone is low-normal. The frequency distribution of the aldosterone/renin ratio is continuous, indicating that PHA is not a discrete abnormality. Indeed, aldosterone-sensitive hypertension is probably a spectrum, with the occasional patient with pure elevation of aldosterone secretion (classical Conn’s syndrome) at one end, and some of the monogenic syndromes with a pure increase in mineralocorticoid receptor response at the other. Most patients probably have inappropriate elevation of both aldosterone secretion and response.

The importance of aldosterone as a cause of resistant hypertension is illustrated in Table 4 which compares the patients at the two ends of the aldosterone/renin ratio distribution. The outstanding difference is in the blood pressure of the two groups of patients. More than half the PHA patients were receiving two or more drugs, and yet had a systolic blood pressure almost 10 mmHg higher than the other groups. When spironolactone was added, blood pressure fell by an average of 27 (systolic)/12 (diastolic) mmHg.

If aldosterone sensitive hypertension turns out to be more polygenic than expected, reducing the likelihood of being due to single discrete variants, the marrying of pharmacological and biochemical phenotypes at least helps to focus on a limited number of candidate genes. Figure 3 illustrates by means of a Venn diagram how the contributions of renin and salt divide hypertension into two overlapping types (with, as already shown, their preferred initial treatments). Apparently resistant hypertension arises in the low-renin, volume-dependent group when aldosterone continues to play a role despite renin being switched off. The gene in which a variant has so far been found is the melanocortin (MC) 5 receptor, for which adrenocorticotropic hormone (ACTH) and alpha melanocyte stimulating hormone (α-MSH) are natural ligands. Among patients meeting our definition for PHA, there was an odds ratio of 1.9 for having a C627G variant of the MC5 receptor, creating a phc→leu substitution. Further study is required to establish what role this plays.

**Single versus combination treatment: long-term benefits?**

Despite the outcome trials and meta-analyses reviewed earlier, the AB/CD schema has met some criticism on the grounds that it underestimates the use of ACE inhibitors in older at-risk patients. In PROGRESS, an ACE inhibitor used alone showed

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**Table 4. The importance of aldosterone as a cause of resistant hypertension. (Patients with high aldosterone to renin ratios have higher systolic and diastolic blood pressures.)**

<table>
<thead>
<tr>
<th>Aldosterone/renin ratio</th>
<th>&gt;800</th>
<th>&lt;400</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61</td>
<td>60</td>
</tr>
<tr>
<td>Blood pressure (mmHg):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>systolic</td>
<td>154</td>
<td>145</td>
</tr>
<tr>
<td>diastolic</td>
<td>92</td>
<td>88</td>
</tr>
<tr>
<td>Sodium (mmol/l)</td>
<td>141</td>
<td>140</td>
</tr>
<tr>
<td>Potassium (mmol/l)</td>
<td>4.0</td>
<td>3.9</td>
</tr>
<tr>
<td>Bicarbonate (mmol/l)</td>
<td>28</td>
<td>28</td>
</tr>
</tbody>
</table>

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**Fig 3. The contributions of renin and salt to hypertension.**

Essential hypertension can be broadly divided into high and low-renin types, in which the major factors are vasoconstriction and volume, respectively. The Venn diagram illustrates the overlapping contribution of these factors in blood pressure (BP) control and how a small number of hypertension phenotypes is compatible with a large number of contributory genotypes. Genes on the left harbour variants more likely to influence high renin hypertension, whilst multiple candidate genes on the right may influence secretion of, or response to, aldosterone (ACTH = adrenocorticotropic hormone; ENaC = epithelial sodium channel; Gsα = alpha subunit of the stimulatory GTP binding protein; 5HT = 5-hydroxytryptamine (serotonin); MSH = melanocyte stimulating hormone).
no significant improvement in outcome, but cardiovascular end-points were reduced by about 30% when it was combined with a diuretic. This is similar to the benefits seen in HOPE in which the ACE inhibitor was added to a range of drugs such as CCBs or nitrates which would activate the renin system.

A post hoc analysis of the blood pressure and outcome data in INSIGHT has suggested that combination treatment achieves the cause-specific benefits of individual drug classes even when blood pressure falls are not additive. In INSIGHT, patients requiring additional drugs had, on average, higher pre- and on-treatment blood pressure than patients controlled on monotherapy (Fig 4). A worse outcome in patients receiving combination therapy might therefore have been predicted, yet the survival was almost identical (illustrated for MI).

We are therefore cautious about concluding from placebo-controlled outcome studies of ACE inhibitors added to other drugs that they are superior to other antihypertensives in older patients. Rather, what may be observed is the cause-specific benefit of ACE inhibitors (eg improvement in endothelial function27–29) on top of any blood pressure reduction. In practice, ACE inhibitors are the only class of antihypertensive drug studied in normotensive, high-risk patients, and therefore other
drug classes cannot be recommended for this group. However, the small falls in blood pressure achieved by the ACE inhibitor in the older patients in HOPE and PROGRESS emphasise the need to combine this class with a diuretic or CCB when blood pressure reduction is the main objective.

Conclusions

We have summarised two different approaches to optimising antihypertensive therapy. The likely role of genetic polymorphisms in guiding the treatment of essential hypertension is as yet unclear, while there is no doubt that knowledge of the genetic basis underpins both understanding and management of patients with the rare single gene disorders causing hypertension.

Rotation studies are a simple – though time-consuming – way of optimising antihypertensive therapy in individual patients. They have also provided good quality data justifying the recognition of three different types of responses:

- to drugs which suppress the renin system
- to drugs with a vasodilator or natriuretic action that activate renin, and
- a dramatic blood pressure response to the aldosterone antagonist spironolactone in patients resistant to other therapies.

An understanding of what drives the increased secretion or response to aldosterone in these patients may either help, or be helped by, discovery of genetic variants in the downstream part of the renin-angiotensin-aldosterone pathway.

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