Drug treatment of hypertension – the future is combination therapy

BRYAN WILLIAMS

Hypertension has long been recognised as a major risk factor for cardiovascular disease, especially stroke. The recent World Health Organisation (WHO) report which examined the major risk factors for global disease identified hypertension as one of the most important causes of the disease burden of developed and developing nations.[1] Importantly, hypertension is easy to detect and amenable to treatment, thereby providing an enormous opportunity to impact favourably on this aspect of global disease risk. Moreover, the evidence base supporting the treatment of hypertension is more extensive than any other in medicine and the findings of many clinical studies have revealed a consistent message: lowering blood pressure (BP) reduces mortality, stroke, coronary heart disease and heart failure.[2] In recognition of the importance of hypertension as a major issue in public health, the Chief Medical Officer for England recently identified hypertension as one of his five priority areas.

Drug treatment of hypertension reduces risk, and the benefits of such therapy are powerfully determined by the quality of BP control achieved. However, the Health Survey for England reported that the percentage of patients achieving a BP goal of < 140/90 mmHg is lamentably low, at around 10%.[2] This means that many preventable cardiovascular events are not being prevented. The same survey also indicates one of the reasons why: clinical trials have consistently demonstrated that most patients with hypertension will require more than one drug to achieve good quality BP control. Put simply, monotherapy for hypertension is inadequate therapy for hypertension. Despite this, only about one third of patients treated for hypertension in the UK receive more than one drug and fewer than 20% receive more than two drugs.[3]

These findings are consistent with 'real-life' reporting from the primary care setting in this supplement by Duggan and Niziol.[4] They report that, in a survey of more than 6,000 hypertensive patients, only 14% reached their BP goal after one year of treatment and that the majority, approximately two thirds, were treated with monotherapy.

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There are many reasons for this undertreatment of BP. Hypertension is largely asymptomatic and many patients are averse to taking multiple drugs. Moreover, managing a clinical condition that affects 20% of the adult population is an enormous burden and is expensive – currently, almost £1 billion per annum is spent in the UK on drugs to treat hypertension. With an ageing population, this figure is set to rise. Apart from these important reasons, I believe the main reasons why BP is not controlled to target in the majority of people are:

1) it is especially difficult to control systolic pressure, and it invariably requires a combination of drugs,[5] and

2) very little guidance has been provided to help physicians define the most effective drug combination for their patients.

In response to this, the British Hypertension Society (BHS) has recently launched its ABCD scheme to improve BP control.[6] We recognised that clear and pragmatic advice was essential to try to standardise and optimise the approach to drug therapy for hypertension in the UK. Wilf Yeo refers to these guidelines on drug combinations in his article in this supplement.[7]

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The ABCD algorithm is based on some very simple principles:

1) Younger people (< 55 years) respond better (in terms of BP reduction) to drugs that block the renin system – this includes 'A' drugs (angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs]), or 'B' drugs (beta blockers). In contrast, older people (> 55 years) or blacks respond better initially to 'C' drugs (calcium channel blockers) or 'D' drugs (diuretics).

2) Most people will require more than one drug, and it is logical to combine A or B with C or D to improve BP control. It is NOT logical at step 2 to combine two drugs from the same group i.e. A+B or C+D. Patients who do not tolerate a drug should be switched to another from the same group, i.e. from a beta blocker to an ACE or ARB.

3) Where possible and when there is no cost disadvantage, at step 2 fixed-dose combinations would be appropriate to reduce the number of medications.

4) This algorithm can be applied to patients with diabetes, almost all of whom will require combination therapy.

It is most likely that, by following this simple schema, many more patients will reach their BP goal and the wasteful prescribing of illogical combinations could be avoided. Further, the hierarchy of prescribing could be better defined. This would greatly assist in the development of 'preferred prescribing practice' lists for the primary care setting, which would in turn improve the efficiency of care for hypertension. An example is given in this supplement.[8] In this regard the ABCD BP-lowering algorithm provides a template to rationalise prescribing in this key area of cardiovascular prevention. Moreover, the ABCD algorithm is not restrictive in that it offers choice within a structured framework.

Angiotensin receptor blockers

Another theme of this supplement is the emergence of the angiotensin receptor blockers, or ARBs, for the treatment of hypertension and other cardiovascular and renal disease. There has been an unprecedented flow of evidence from clinical trials supporting the safety and efficacy of this class of drugs. Many more data are soon to emerge to clarify further the role of ARBs in the treatment of hypertension, and the management of patients with heart failure and post-myocardial infarction. This will be important since ARBs have become popular drugs because of their impressive tolerability and flexibility in combining effectively with diuretics and/or calcium channel blockers (CCBs). This flexibility is important, and the emergence of fixed-dose combinations of ARBs with a thiazide diuretic is welcomed and long overdue in the UK.

Combinations of ACE-inhibitors or ARBs with a thiazide diuretic are likely to form the backbone of effective antihypertensive therapy, with a CCB added in the substantial number of those who fail to achieve target BP. The fact that this powerful triple therapy combination could be delivered as only two drugs could revolutionise the quality of BP control in the UK and beyond.[9,10]

References

1. Ezzati M, Lopez AD, Rodgers A, Vander Hoom S, Murray CJ. Selected major risk factors and global and regional burden of disease. *Lancet* 2002;**360**:1347-60.
2. Collaboration Blood Pressure Lowering Treatment Trialists. Effects of angiotensin converting enzyme inhibitors, calcium antagonists and other blood pressure lowering drugs on mortality and major cardiovascular morbidity. *Lancet* 2000;**356**:1955-64.
3. Primatesta P, Brookes M, Poulter NR. Improved hypertension management and control: results from the Health Survey for England 1998. *Hypertens* 2001;**38**:827-32.
4. Duggan AK, Niziol CJ. Real-life treatment of hypertension in UK primary care: prescribing habits, results and adherence to clinical guidelines. *Br J Cardiol* 2003;**10**(suppl 3):3-7.
5. Mancia G, Grassi G. Systolic and diastolic blood pressure control in antihypertensive drug trials. *J Hypertens* 2002;**29**:1461-4.
6. Brown MJ, Cruickshank JK, Dominiczak AF *et al*. Better blood pressure control: how to combine drugs. *J Hum Hypertens* 2003;**17**:81-6.
7. Yeo W. The role of angiotensin receptor blockers in hypertension. *Br J Cardiol* 2003;**10**(suppl 3):8-14.
8. Yassaie M. Introduction of valsartan into the 'preferred prescribing practice' list for Wokingham PCT. *Br J Cardiol* 2003;**10**(suppl 3):15-17.
9. Williams B. Drug treatment of hypertension. *BMJ* 2003;**326**:61-2.
10. Williams B. Treating hypertension: It is not how you start but where you end that matters. *J Hypertens* 2003;**21**:1-3.

Real-life treatment of hypertension in UK primary care: prescribing habits, results and adherence to clinical guidelines

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Abstract

Recent UK hypertension guidelines from the British Hypertension Society have placed increased importance on antihypertensives that work on the renin-angiotensin system (RAS). There is also an explicit acknowledgement that for many patients monotherapy will be insufficient to achieve hypertensive control. This study aimed to examine antihypertensive prescribing in the UK through an analysis of 6,861 primary care patient records and to compare prescribing patterns with hypertension guidelines. The effects on blood pressure were also examined.

Only 14% of patients achieved normotension after 12 months of treatment; and after 12 months the severity of hypertension did not improve in 39% of diabetic patients. The majority (65%) of severely hypertensive patients were treated with only one agent. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers were under-utilised in diabetics both as first-line and add-on therapy, and therapy choices for additions/switches correlated with guidelines in fewer than 40% of cases.

This study shows that there is room for improvement in UK hypertension management, in particular with regard to consideration of co-morbidity in first-line treatment, use of combination rather than monotherapy, and more appropriate additions/switches from first-line therapy as advocated by clinical guidelines.

Key words: hypertension, retrospective studies, disease management, blood pressure, antihypertensive agents, UK.

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Introduction

The majority of hypertensive patients do not have their blood pressure (BP) adequately controlled by any single agent.[1,2] Many patients require multiple changes to their original prescription and even then, few are successfully treated to published target levels of BP.[3,4] Diabetic patients are more likely to develop hypertension and appear to be more susceptible to the adverse consequences of raised BP.[5,6] Treating high BP in diabetic patients generates significant health gains.[7] Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists/blockers (ARBs) have a particular value in diabetic patients, having been shown to reduce the development of nephropathy.[8]

Revised guidelines for the management of hypertension in the UK were recently published.[9] These recommend the adoption of what has been called the AB/CD rule.[9] Table 1 describes the simple rationale of this proposed treatment pathway.

Thus calcium channel blockers (CCBs) and diuretics are suggested as first-line therapy in the older population (> 55 years) and ACE inhibitors (ACE-Is), ARBs or beta blockers as first-line treatment in the younger population. These guidelines also imply a lesser role for beta blockers, as their inclusion early in treatment prevents accurate adherence at step three without their discontinuation.

The National Institute for Clinical Excellence (NICE) published its guidelines dedicated to the management of hypertension in diabetic patients in 2002.[10] Table 2 outlines the main advice from these guidelines.

Guidelines for the treatment of hypertension have been available to UK clinicians since publication of the British Hypertension Society (BHS) guidelines in 1993.[11] However, there is uncertainty as to the degree to which guidelines are adopted in clinical practice.

Table 1. BHS recommendations for a stepped approach in BP reduction[9]

	Younger (< 55 years) and non-black patients	Older (> 55 years) or black patients
Step 1	A or B	C or D
Step 2	A or B + C or D	
Step 3	A + C + D	
Step 4	Add either: beta blocker, spironolactone or another diuretic	

Key: A = ACE inhibitor or ARB; B = beta blocker; C = calcium channel blocker; D = diuretic

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Table 2. NICE guideline for the management of hypertension in diabetes[10]

	Diabetic patient	Diabetic with evidence of reduced renal function
Recommended drug class for first-line treatment (in the order of appearance)	ACE inhibitor ARB Beta blocker Thiazide	ACE inhibitor or ARB
Specific warnings	CCBs should only be used as second line or in combination	

Objective

The objective of this study was to assess the major prescription treatment pathways and to evaluate the real-life effectiveness of current antihypertensive prescribing in the UK.

Methods

This analysis was based on prescribing data from GP computer systems that were part of the DIN-LINK network.[12] We identified the medical records of newly diagnosed patients with hypertension who were first treated between 1999 to 2001, and we followed patients up for a total of 12 months. From the electronic patient records, we analysed information on drug choice, drug combination, number of days of treatment per prescription and resulting BP. From these data we sought to identify which aspects of current prescribing were not in concordance with published guidelines or were not achieving target levels of BP.

We used published NICE guidance[10] and guidelines from the BHS[9,13] to define appropriate prescribing behaviour. The BP target levels of 140/85 mmHg for non-diabetic patients and 140/80 mmHg for diabetic patients were taken from recommendations of the BHS.[13]

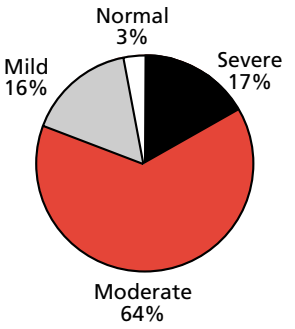
Results

Patient characteristics

A total of 10,716 patients satisfied the inclusion criteria. Of these patients, 6,861 records had BP readings available both at the start of treatment and 12 months later, and were included in the study. The average age of patients was 63 years (SD 13.4) and 46% of patients were male. Thirty five per cent of patients had a significant co-morbidity (diabetes, myocardial infarction [MI], angina, heart failure, asthma, chronic obstructive pulmonary disease [COPD]) that would have been expected to influence treatment selection.

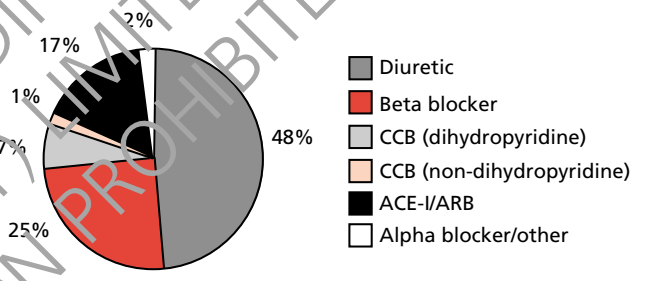
Based on BHS definitions,[13] at the time of treatment initiation 17% of patients were classed as having severely raised BP (≥ 200/110 mmHg), 64% had moderate hypertension (160–199/100–109 mmHg), 16% had mildly raised BP (140–159/90–99 mmHg) and 3% of patients were recorded as normotensive (≤ 139/89 mmHg) (figure 1). The overall mean systolic BP at treatment initiation was 169.5 mmHg (± 21.1 mmHg) and the mean diastolic BP was 96.0 mmHg (± 11.8 mmHg).

Figure 1. Blood pressure severity at diagnosis in this study



Definitions of hypertension taken from BHS guidelines[13]

Figure 2. First-line choice of therapy in this study



Key: ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker

Choice of first-line therapy

The most commonly prescribed first-line agent was a diuretic (48%), followed by a beta blocker (25%). Together these two classes made up almost three quarters of first-line treatment (see figure 2). This prescribing behaviour is highly consistent with the BHS recommendations at the time of the analysis, that diuretics and beta blockers should be the first-line agents unless a patient's co-morbidities dictated a different choice.

Co-morbidity had a significant effect on choice of first drug. Patients with diabetes were most commonly initiated on an ACE-I or ARB (60%). ACE-Is or ARBs were also used more in patients post-MI or with heart failure. Beta blocker usage was increased in angina and post-MI, and decreased in patients with diabetes and heart failure. Patients with asthma and COPD had beta blockers prescribed to them at unexpectedly high rates (12% and 7%, respectively). The choice of first-line monotherapy is shown in table 3.

Changes from first-line therapy

The majority of patients experienced some alteration to their original prescription during the first 12 months of treatment.

Table 3. Choice of first-line monotherapy in relation to co-morbidity

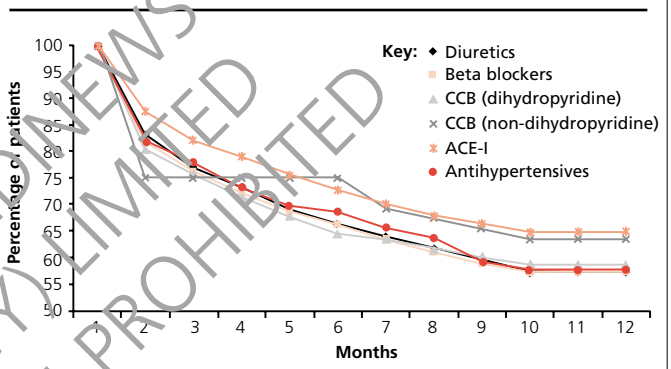
First-line agent	Diabetes (n=882; 11.9%)	Angina (n=338; 4.6%)	MI (n=181; 2.5%)	CHF (n=88; 1.2%)	Asthma (n=812; 11.0%)	COPD (n=285; 3.9%)	Total (n=7,386)
Diuretic	20%	39%	33%	43%	51%	59%	48%
Beta blocker	12%	30%	29%	10%	12%	7%	25%
CCB	6%	14%	10%	12%	14%	16%	8%
ACE-I/ARB	60%	14%	24%	26%	21%	15%	17%
Alpha blocker/other	2%	2%	4%	8%	2%	2%	2%

Key: MI = myocardial infarction; CHF = cardiac failure; COPD = chronic obstructive pulmonary disease; CCB = calcium channel blocker; ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker

Table 4. Major drug changes after initial treatment

Initial drug	Most commonly switched to	Most common drug added
Diuretic	Beta blocker	Beta blocker
Beta blocker	Diuretic	Diuretic
Calcium channel blocker	Diuretic	ACE-I
ACE inhibitor	ARB	Diuretic
Other	Diuretic	Diuretic/beta blocker

Figure 3. Continuation rates for each first-line monotherapy drug class 12 months after treatment initiation



Key: CCB = calcium channel blocker; ACE-I = angiotensin-converting enzyme inhibitor

These changes were either change of agent, the addition of a second agent or dose changes. The major drug class switch and add-in decisions are shown in table 4.

Ten per cent (n=671) of patients had a switch in treatment during the first year of therapy and 20% (n=1,350) had a drug added to their treatment. Eighteen per cent (n=1,257) of patients had a dose adjustment.

After one year of treatment this resulted in 17% being on no antihypertensive drugs, 56% on one drug, 23% on two drugs and 4% on three or more.

The BHS (1999)[13] recommended a number of combinations of antihypertensive therapy with complementary modes of action, namely diuretic plus ACE-I, diuretic plus beta blocker, beta blocker plus CCB and CCB plus ACE-I. The BHS recommends that if a patient is intolerant of a drug or if the drug has minimal effect then the drug should be stopped and a drug of a different class should be initiated.

Prescription guidelines that were prevalent during the period of study[13,14] were not adhered to in 39% of drug changes and 36% of drug combinations. Examination of prescription data against the updated BHS guidelines[9] shows 26% of drug combinations and 75% of drug changes to be in line with recommendations.

Perversely, 13% of all drug changes and 6% of drug additions were within the same class as the original drug: for example, one diuretic was added to another or a patient receiving a beta blocker was switched to another beta blocker. Amongst patients with diabetes the next logical choice after discontinuing an ACE-I would be an ARB, yet this choice was made for only 50% of such patients. Of those who were not switched to an ARB, the most common choice was a switch to a CCB.

Continuation rates

Diuretics and beta blockers had the worst rates of continuation, with almost 20% of patients stopping treatment after just one month. As in most other such analyses,[3,15] ACE-Is were associated with the greatest continuation rates in this study: here 65% of patients continued with their initial prescription. Continuation rates for each drug class are shown in figure 3. Although no ARBs were used as first-line agents in this dataset, evidence suggests that ARBs have improved tolerance compared to other antihypertensive classes. This improved tolerance has been demonstrated to translate into increased continuation rates.[16]

BP control

Only 14% of patients had their BP adequately controlled after 12 months of treatment. This was despite the typical patient being prescribed a number of different agents, either sequentially or in

Table 5. Level of BP control at one year and number of drugs prescribed

	Number of drugs				
Blood pressure	**0**	**1**	**2**	**3**	**4+**
Normalised	17%	59%	20%	3%	1%
Mild	15%	59%	23%	3%	0%
Moderate	20%	51%	24%	4%	1%
Severe	21%	44%	24%	9%	2%

combination. Whilst 66% of patients moved down one band of BP severity or more, 31% experienced no change and 4% moved to a higher band. In other words, 35% of patients experienced no substantial benefit from 12 months' treatment of hypertension and 86% did not have their BP normalised. Patients with diabetes fared slightly worse, with 61% improving, 33% experiencing no change and 6% worsening. A high proportion of patients with moderate to severe hypertension were only receiving one agent (65%) or two agents (28%) at 12 months.

After 12 months of treatment the average BP reading in diabetic patients was 156/85 mmHg, with 45% having moderately to severely raised BP and only 14% being treated to target. The average BP for all patients was 148/85 mmHg after 12 months. The level of BP control after 12 months according to the number of drugs prescribed is shown in table 5.

The impact of switching and drug combinations on BP

Changes in agent resulted in very modest improvements in BP control. Thirteen per cent of all drug changes and 6% of additions were within the same class as the original drug. BP reductions were greatest when new drugs were added and smallest when an intra-class switch occurred. Intra-class switching resulted in a < 3/2 mmHg fall in BP. The data demonstrate that the most effective way to reduce BP is to add a drug from a different drug class, rather than to switch drug or add a drug within the same class.

Amount of drug prescribed

The average number of days of treatment available per patient per year was 284, or 77% of the year; 29% of patients received fewer than 200 days of prescription per year.

Discussion

Data about BP and its treatment that are extracted from patient notes are subject to two major sources of error – under-recording of data (as found in this study) and inaccuracy of BP readings. Interpretation of such data faces further challenges since no account can be made for the confounding effects of weight change and concomitant diseases and their treatment. It is known, for example, that there is a 'white coat' effect when BP is being recorded.

However, the strength of this type of analysis is that large numbers of patient records can be considered. What is very pertinent from this study is that the recorded BP levels were the ones that GPs were using for their prescribing decisions. Thus the widespread existence of moderate to severe hypertension in the presence of low levels of prescribing is concerning.

Published guidelines are not always followed when clinicians choose first-line drug treatment: there are many errors and missed opportunities. This is most evident in diabetic patients, of whom only 60% receive the recommended ACE-I or ARB classes of drug as first-line treatment.

The majority of patients require changes to their initial drug therapy, due either to lack of BP control or to the emergence of adverse events. Almost 40% of the changes made in this study were not in line with published guidelines. Approximately 10% of these changes involved the use of drugs within the same class. Such intra-class switching and intra-class combinations have little physiological or pharmacological basis and cause insignificant reductions in BP.

The consequences of continuously raised BP are significant. These patients almost certainly have avoidable morbidity and mortality, with a commensurate impact on NHS resources. The majority of hypertensive patients continue to live with raised BP, resulting in elevated risk for cardiovascular disease.

Recently National Service Frameworks (NSF) have become key drivers of policy in the NHS. The attainment of the standards specified in the NSF for CHD[17] appears to be a challenge. There is a need for a concerted and planned approach to the management of hypertension. This is likely to require an increase in funding to facilitate the required increase in appropriate prescribing.

Conclusions

These data demonstrate that as many as 86% of hypertensive patients in the UK should have their BP management reviewed and more intense treatment considered, e.g. through adding an extra drug. The majority of those who continue to have even moderately to severely raised BP are prescribed only one or two agents – despite evidence that multiple drug therapy can generate increasing levels of BP control.

Patients with diabetes are particularly at risk of developing cardiovascular events when they have raised BP, and it has been shown that intensive treatment can generate significant health gains in this group. Despite this, we found that patients with diabetes were no better controlled or more intensively managed than other patient groups.

New hypertension guidelines[9] introduced after these data were gathered will support physicians in their efforts to reach targets for hypertension management. The guidelines recommend strategies for rational prescribing of multiple drug therapy for hypertension, and these should help to increase the proportion of patients achieving their BP targets.

Physicians may need to employ a number of techniques to monitor and improve compliance in patients with hypertension. Particular effort must then be made to simplify dosing schedules and to increase the use of those drugs that are associated with a low frequency of adverse events.

Key messages

- In this study only 14% of patients were treated to target BP at 12 months
- 35% of patients did not show improvement in BP control after 12 months of treatment. This figure increased to 39% in diabetics
- 65% of patients with severe hypertension were taking only one agent, or were untreated, at 12 months
- Only 60% of diabetics received a RAS inhibitor as first-line treatment

Editors' note

It is with regret that the journal records the recent death of Mr Andrew Duggan.

References

1. Materson BJ, Reda DJ, Cushman WC. Department of Veterans Affairs single-drug therapy of hypertension study. Revised figures and new data. Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *Am J Hypertens* 1995;**8**:189-92.
2. Hansson L, Zanchetti A, Carruthers SG *et al*. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998;**351**:1755-62.
3. Jones JK, Gorkin L, Lian JF, Staffa JA, Fletcher AP. Discontinuation of and changes in treatment after start of new courses of antihypertensive drugs: a study of a United Kingdom population. *BMJ* 1995;**311**: 293-5.
4. Primatesta P, Brookes M, Poulter NR. Improved hypertension management and control: results from the Health Survey for England 1998. *Hypertension* 2001;**38**:827-32.
5. Feher MD. Hypertension in diabetes. *Pract Diabetes Internat* 2001; **18**:197-200.
6. Mehler PS, Coll JR, Estacio R, Esler A, Schrier RW, Hiatt WR. Intensive blood pressure control reduces the risk of cardiovascular events in patients with peripheral arterial disease and type 2 diabetes. *Circulation* 2003;**107**:753-6.
7. Grossman E, Messerli FH, Goldbourt U. Review: Intensive blood pressure control and drugs reduce morbidity and mortality in hypertension and diabetes mellitus. *Evidence-Based Medicine* 2001;**6**:44-7.
8. Kassianos G. Optimising management of patients with hypertension and diabetes. *Br J Cardiol* 2002;**9**:297-302.
9. Brown M, Cruickshank J, Dominiczak A, MacGregor G, Poulter N, Russell G. Better blood pressure control: how to combine drugs. *J Hum Hypertens* 2003;**17**:81-6.
10. National Institute for Clinical Excellence. *Clinical guidelines for type II diabetes; blood pressure management*. Sheffield: Royal College of General Practitioners. Effective clinical practice unit, 2001:1-145.
11. Sever P, Beevers G, Bulpitt C *et al*. Management guidelines in essential hypertension: report of the second working party of the British Hypertension Society. *BMJ* 1993;**306**:983-7.
12. DIN-Link database: Compufile Ltd. www.compufile.co.uk.
13. Ramsay L, Williams B, Johnston G *et al*. Guidelines for management of hypertension: report of the third working party of the British Hypertension Society. *J Hum Hypertens* 1999;**13**:569-92.
14. Lip G, Beevers M, Beevers D. The 'Birmingham Hypertension Square' for the optimum choice of add-in drugs in the management of resistant hypertension. *J Hum Hypertens* 1998;**12**:761-3.
15. Caro JJ, Speckman JL, Salas M, Raggio G, Jackson JD. Effect of initial drug choice on persistence with antihypertensive therapy: the importance of actual practice data. *CMAJ* 1999;**160**:41-6.
16. Wogen J, Charles A, Kreilick A, Livornese R, Frech F. A population-based study of compliance and persistency with cardiovascular agents used in hypertension management. *Am J Hypertens* 2001;**14**(suppl 1):112a-115a.
17. NSF. National Service Framework for Coronary Heart Disease. London: Department of Health, 2000.

The role of angiotensin receptor blockers in hypertension

WILF W YEO

Abstract

Angiotensin receptor blockers (ARBs) are efficacious in terms of reducing blood pressure in hypertensive patients. With a placebo-like side-effect profile, the adherence to drugs in this class is higher than with other antihypertensive agents. Recent trials have demonstrated the benefit of ARBs in hypertensive patients with diabetes, and the benefit of ARBs in regressing left ventricular hypertrophy. Research is currently being carried out to evaluate whether ARBs are beneficial in the treatment of patients with heart failure and after myocardial infarction. This article reviews the evidence underlying the use of ARBs in clinical practice, in view of the recent British Hypertension Society (BHS) recommendations for their use in the UK.

Key words: hypertension, angiotensin receptor blockers, antihypertensives, diabetes, nephropathy, left ventricular hypertrophy, heart failure.

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Introduction

Hypertension remains one of the most important causes of preventable premature deaths worldwide,[1] and the benefits of antihypertensive treatment have been confirmed by many large outcome studies. A number of distinct drug classes can be used to lower blood pressure (BP), and over the past 20 years there has been much debate regarding the relative merits of treatment with each of the major drug classes – thiazide diuretics, beta blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors and alpha blockers. One key question is whether older drugs such as thiazides and beta blockers are as effective as the more modern drugs. The two most recent studies, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[2] and the Second Australian National Blood Pressure Study (ANBP2),[3] have given somewhat conflicting results on the relative merits of the different drug classes.

In this paper we describe the place of angiotensin receptor blockers (ARBs) in hypertension management and discuss how their use compares with other major drug classes.

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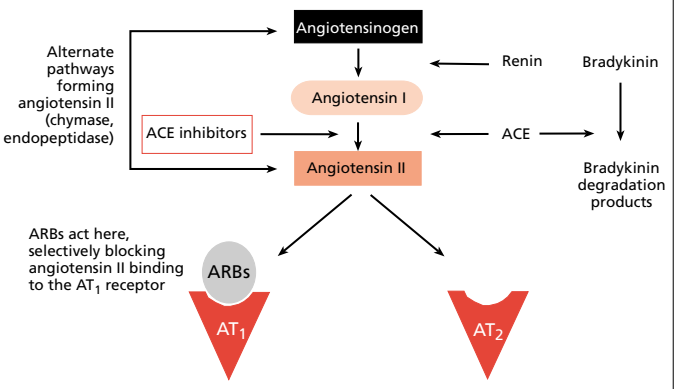
Efficacy of antihypertensive agents

The BP-lowering efficacy of the commonly used antihypertensive classes is broadly similar.[4] The expected reduction from a single agent is in the range of 10–15 mmHg for systolic BP and 7–9 mmHg for diastolic BP. The alpha blockers are probably less effective as antihypertensive agents.[4,5]

ARBs block the angiotensin 1 receptor, which mediates vasoconstriction and has some effects on aldosterone secretion (figure 1). A meta-analysis of the effects of losartan, valsartan, irbesartan and candesartan in 43 randomised controlled trials treating more than 11,000 patients reported a BP reduction for the drug class of 10.8/8.5 mmHg at their starting doses, and 13.3/9.9 mmHg when titrated through the dose range according to patient response.[6]

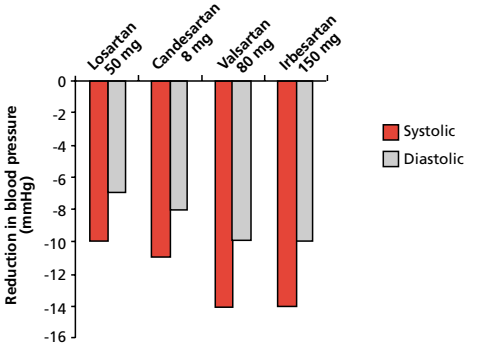
Within the class there is a range of responses, although it appears that losartan (the first drug to be developed) is generally less effective at lowering BP than the newer agents in the class, such as valsartan, irbesartan and candesartan.[7] In a double-blind, cross-over study, losartan 50 mg daily lowered BP by an average of 10/7 mmHg, compared to 11/8 mmHg for candesartan 8 mg,

Figure 1. The renin-angiotensin system and site of action of ARBs



Key: ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blocker

Figure 2. Blood pressure-lowering efficacy in hypertensive patients in a comparative cross-over study of ARBs



Adapted from Fogari *et al.* A double-blind, cross-over study of the antihypertensive efficacy of angiotensin II receptor antagonists and their activation of the renin-angiotensin system. *Curr Ther Res* 2000;**61**:669-79.[7]

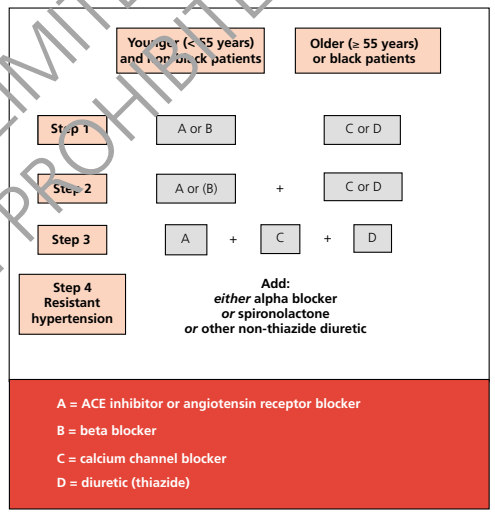
and 14/10 mmHg for both irbesartan 150 mg and valsartan 80 mg daily (figure 2). The differences in BP of 2/3 mmHg between irbesartan and valsartan when compared to losartan were statistically significant ($p<0.05$). The authors calculated the equipotent doses for the four ARBs as 80.5 mg for losartan, 13.7 mg for candesartan, 216.6 mg for irbesartan and 115.5 mg for valsartan. These doses represent 81% of the maximum recommended dose for losartan (100 mg), 85% for candesartan (16 mg) and 72% for both irbesartan (300 mg) and valsartan (160 mg).

Antihypertensive drugs used in combination

It is now well established that multiple drug therapy is required for the majority of hypertensive patients to achieve the currently recommended BP goals. Ideally, antihypertensive agents used in combination should have maximum efficacy with the minimum of side effects. There is growing evidence that drugs inhibiting the renin-angiotensin system (RAS), such as ARBs, ACE inhibitors (ACE-Is) and beta blockers, should be prescribed with classes that have different BP-lowering mechanisms (diuretics and calcium channel blockers), to produce a synergistic action that lowers BP. Two UK centres applying this approach to logical combinations of antihypertensive drugs have developed the Birmingham Hypertension Square[8] and the AB/CD rule for hypertension management.[9,10]

This rational approach to drug combinations has prompted the Executive Committee of the British Hypertension Society (BHS) to issue new guidelines on how to combine drugs for better BP control.[11] The recommendations (figure 3) are based on the likely renin level of the patient needing treatment. On average, young white patients tend to have higher renin and angiotensin II levels, so for these patients a drug acting on the RAS is recommended. Older and black patients tend to have lower renin and angiotensin II levels so calcium channel blockers or thiazides are advised for them (figure 3). There is a trend away

Figure 3. The British Hypertension Society recommendations for a simplified approach to blood pressure-lowering therapy



Adapted from Brown MJ *et al.* Better blood pressure control: how to combine drugs. *J Hum Hypertens* 2003;**17**:81-6.[11]

from beta blockers, especially for older patients in whom the risk of new onset diabetes mellitus with a combination of beta blockers and diuretics is significant, as seen in the Losartan Intervention for Endpoint reduction in hypertension (LIFE) study.[12] If two-drug therapy fails to control the BP to target (< 140/85 mmHg, and lower in diabetes), then standard three-drug treatment for hypertension should include an ACE-I or ARB, a calcium channel blocker and a thiazide diuretic (A + C + D; figure 3).

Adherence to treatment

Mild hypertension is a chronic condition with no symptoms.

Therefore, for a patient to benefit from the cardiovascular protection offered by antihypertensive therapy adherence with treatment is fundamental. There are many factors that affect compliance with therapy, including the doctor-patient relationship, the patient's education, the number of medications prescribed and the tolerability of the drugs. In the largest outcome trial in hypertension, ALLHAT,[2] 16% of patients randomised to chlorthalidone had discontinued the study drug by the one-year visit, compared to 17% for amlodipine and 23% for lisinopril. By the five-year visit the percentage of patients who had discontinued the study drug was 28% for amlodipine, 30% for chlorthalidone and 38% for lisinopril.

The recent Second Australian National Blood Pressure Study compared ACE-Is and diuretics as antihypertensive drugs in the elderly. The study was a prospective, open-labelled, blinded end points (PROBE) design, and patients were followed for a mean of 4.1 years. Family practitioners were responsible for BP management, that had to conform to the drug class randomisation and BP goals.[3] Enalapril and hydrochlorothiazide were the study drugs recommended, but family doctors could choose another agent within the class. In this open-label study the discontinuation rates at about four years were 38% for the diuretic group and 42% for the ACE-I group.

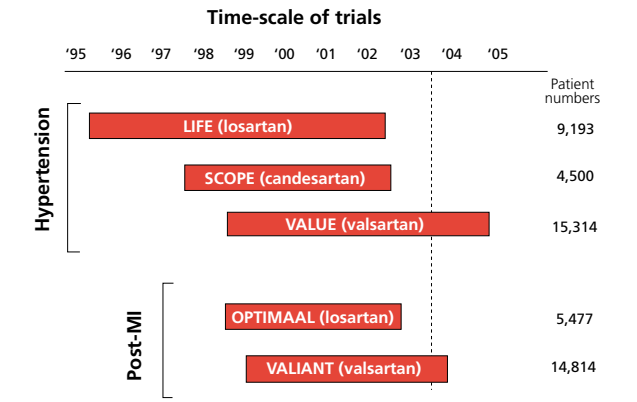
How do ARBs compare with the other major drug classes? One strength of the ARBs is that they appear to have a placebo-like side-effect profile. For example, patients are not troubled by the peripheral oedema and cough associated with calcium channel blockers and ACE-Is. When data from various studies have been pooled and examined, the side-effect profiles of the ARBs have not been significantly different from those of placebos.[13-15]

There is some evidence to suggest that this advantage in tolerability is translated into increased adherence with therapy. In observational studies of ordinary practice, the proportion of patients remaining on the initial antihypertensive treatment varies from 38% to 64% after one year.[16] A study reflecting practice in the UK suggested that continuation rates of initial antihypertensives were as low as 50% at six months.[17] The discontinuation of drugs in ordinary practice is subject to patient and doctor bias regarding drug side effects and perceived efficacy. Nevertheless, the ARB class is consistently reported as the class with greater patient adherence when compared to diuretics, beta blockers, calcium antagonists and ACE-Is. One representative study reported a significantly greater proportion of patients continuing therapy at one year when treated with valsartan (66%) compared to both lisinopril (55%) and amlodipine (57%).[18]

Mortality and morbidity data in hypertension

Diuretic- and beta blocker-based stepped-care therapy for hypertension has secured a strong evidence base for mortality and morbidity benefits, and has been the recommended first-line treatment in the UK and northern Europe for some years. Recently, for the first time since those initial trials in hypertension, a newer drug class has been shown to be superior to one of these standard therapies. The LIFE study[12] compared losartan to atenolol in 9,192 high-risk hypertensive patients with left ventricular hypertrophy (LVH). It showed that, for a similar level of BP control, losartan reduced cardiovascular mortality and morbidity by 13% and – importantly – stroke by a further 25% compared to atenolol. This trial suggests that outcome, in some groups of patients, does depend on the agent used and not solely on the lowering of BP.

Figure 4. Major outcome trials with ARBs in hypertension and after myocardial infarction



Key: ARB = angiotensin receptor blocker; MI = myocardial infarction

The Study on Cognition and Prognosis in the Elderly (SCOPE)[19] compared the effects of candesartan-based therapy and placebo in elderly patients (70–89 years) with mild hypertension. There was no significant difference between the groups for the primary end point of combined cardiovascular events (cardiovascular death, myocardial infarction [MI] and stroke). One of the secondary end points demonstrated 28% fewer strokes in patients treated with candesartan.

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial,[20] which is due to report in 2004, is comparing the effects of valsartan and amlodipine on cardiovascular mortality and morbidity in 15,314 high-risk hypertensive patients. Entry to the trial was dependent on age and a combination of risk factors and coexisting diseases, including LVH. VALUE has recruited a population of patients with a broad range of characteristics (LVH 12%, type 2 diabetes 32%, coronary heart disease 46%, stroke 21%) and thus the results should be applicable to many patients with hypertension (figure 4).

Diabetes and blood pressure

The presence of diabetes mellitus profoundly increases cardiovascular risk, and diabetic patients generally have higher BPs and worse lipid profiles than non-diabetic subjects.[21,22] One serious complication that occurs commonly in type 1 diabetes is the development of microalbuminuria, followed by overt nephropathy. The level of BP and degree of proteinuria strongly predict the development of diabetic nephropathy. Drugs that lower BP have all been successful in slowing the progression of diabetic nephropathy, but ACE-Is have a pivotal role. They decrease the

rate of progression from microalbuminuria to clinical proteinuria and, once proteinuria is established, ACE-Is also significantly reduce the risk of death, or the need for dialysis or renal transplantation.[23]

In type 1 diabetes ACE-Is offer renoprotection in hypertensive and normotensive patients with microalbuminuria.[24] In type 2 diabetes the role of ACE-Is is less established. A BP reduction of about 10/5 mmHg with either beta blocker- or ACE-I-based treatment afforded patients in the United Kingdom Prospective Diabetes Study (UKPDS) significant protection against the complications of diabetes.[25] In the Heart Outcomes Prevention Evaluation (HOPE) study[26] ramipril was used in individuals at high cardiovascular risk, including a cohort of diabetic patients, with no pre-determined BP threshold for recruitment. In diabetic patients ramipril reduced mortality and cardiovascular end points by 25% over 4.5 years of follow-up.[27]

ALLHAT did not confirm an advantage for diabetic patients randomised to lisinopril versus those assigned to chlorthalidone,[2] who on average had an 8% lower rate of cardiovascular disease. However, the chlorthalidone group did achieve a 2 mmHg lower systolic pressure and this probably accounts for the small difference in outcome. The recent ANBP2 was a smaller study,[3] and although it showed an advantage for older men on an ACE-I, it may not have sufficient power to analyse the diabetic cohort separately.[3]

ARBs and diabetes

A number of recent trials have demonstrated the benefit of ARBs in hypertensive patients with type 2 diabetes. As with ACE-Is, the trials have focused on diabetics with varying degrees of renal dysfunction.

Type 2 diabetes and microalbuminuria

Two large studies have assessed the effects of ARB therapy on renal function in type 2 diabetes patients with coexistent hypertension and microalbuminuria. In one study, 590 patients with type 2 diabetes and microalbuminuria were randomised to irbesartan 150 mg or 300 mg or to placebo and followed up for two years.[28] Patients were treated to a BP target of 135/85 mmHg. The higher dose of irbesartan reduced the risk of progression to nephropathy significantly by 70% ($p<0.001$) and reduced the urinary albumin excretion rate (UAER) by 38%. Irbesartan 150 mg did not significantly reduce the risk of nephropathy but reduced UAER by 24%.

In the MicroAlbuminuria Reduction with VALsartan (MARVAL) study, 332 patients with type 2 diabetes and microalbuminuria were randomised to valsartan 80 mg or amlodipine 5 mg and followed for six months.[29] If patients were not controlled to the 135/85 mmHg target, the dose of the medication was doubled before diuretic or alpha blocker therapy was introduced. At the end of the study period both treatment groups had similar BP control, at 135/78 and 136/79 mmHg. In the hypertensive valsartan group, the UAER was reduced by 47% compared to baseline, whereas amlodipine only reduced the albumin excretion rates by 11%. This difference was highly significant, $p<0.001$. These studies suggest that ARBs effectively reduce albumin excretion and progression to nephropathy independent of the simple BP-lowering effect.

Type 2 diabetes and nephropathy

In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial, which studied 1,513 patients with type 2 diabetes and established nephropathy, participants were randomised to either losartan 50 mg or placebo and were followed for an average of 3.4 years.[30] The BPs were treated to a goal of 140/90 mmHg by doubling the dose of the study drug and then adding alternative therapies. The primary composite end point of doubling of serum creatinine, end-stage renal disease (ESRD) or death was reduced by 16% in the losartan group compared to placebo ($p=0.02$). As regards the elements of this composite end point, there was a 25% reduction for doubling of serum creatinine and a 28% reduction for the development of ESRD. The death rate, however, was not reduced significantly.

A similar trial randomised 1,715 patients with type 2 diabetes and nephropathy to irbesartan 300 mg, amlodipine 10 mg or placebo.[31] Therapies other than ARBs, ACE-Is or calcium antagonists were used to treat towards a target BP of 135/85 mmHg. The mean duration of follow-up was 2.6 years. The composite end point of doubling of serum creatinine, end-stage renal failure or death was reduced in the irbesartan group by 20% ($p=0.02$) compared to placebo and by 23% compared to amlodipine. There was no significant difference in the rate of death or ESRD between the groups, again the largest effect was in the relative risk reductions for doubling of serum creatinine, which was reduced by 33% in the irbesartan group versus placebo ($p=0.003$) and by 37% versus amlodipine ($p<0.001$).

In summary, for type 1 and type 2 diabetes the key appears to be to control BP tightly. When complications are already present, treatment should be based on drugs that reduce cardiovascular complications. When albuminuria or nephropathy is present, hypertensive patients should be treated with drugs working through the RAS. As described above, recent studies show that ARBs slow the progression of diabetic nephropathy in type 2 diabetes to a greater degree than other drug classes with equal BP control. ARBs are probably equal to ACE-Is for renoprotection.[32]

Left ventricular hypertrophy

LVH is found often in the hypertensive population and is primarily a compensatory response to the increased workload. This has been reported in up to 50% of patients with mild to moderate hypertension at a referral centre and up to 90% of hospitalised patients.[33,34] LVH is an independent predictor of cardiovascular outcomes:[35] most antihypertensive agents reduce left ventricular mass but not all agents are considered equipotent. A meta-analysis of randomised double-blinded studies revealed that ACE-Is reduced the left ventricular mass index (LVMI) by 13%, compared to 9% for calcium channel blockers, 7% for diuretics and 6% for beta blockers.[36]

Current understanding of the functions of the ARBs supports

the hypothesis that RAS-blocking drugs are particularly effective in regressing LVH. Indeed, in separate trials when irbesartan and valsartan were compared with atenolol, both demonstrated 17% reductions in LVMI, which were greater than the effect of atenolol.[37,38] When valsartan 80 mg and enalapril 20 mg were compared, the LVMI was reduced by similar proportions, at 20% and 22% respectively.[39]

ARBs for cardiovascular protection

ARBs are not currently licensed for cardiovascular protection in the UK for patients in heart failure, or after MI. Research is being carried out to determine whether ARBs would benefit these patient groups.

Following myocardial infarction

ACE-Is improve survival and reduce the rates of reinfarction and heart failure, and also limit the size of the infarct. Thus ACE-Is are regarded as first-line treatment in these patients. However, despite ACE-I therapy serious complications remain common. During ACE blockade angiotensin II continues to be produced at both a tissue level and via alternative enzymes so theoretically blockade of the RAS at the receptor level with an AT_1 receptor blocker is an attractive concept.

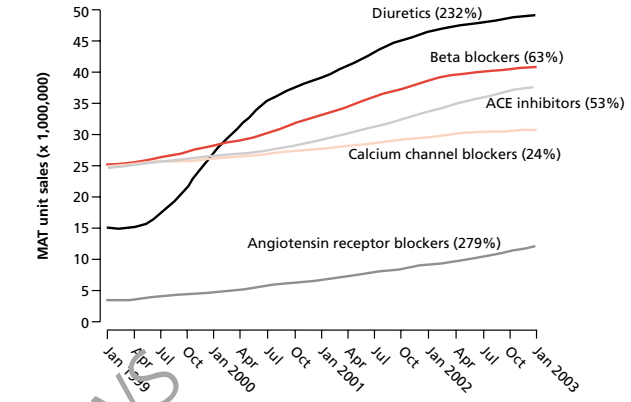
The first study to explore this was the Optimal Therapy in Myocardial infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) study.[40] In this trial, 5,477 post-MI patients with signs or symptoms of heart failure were randomised to either losartan 50 mg o.d. or captopril 50 mg t.d.s. The non-significant difference in mortality in favour of captopril suggested that ACE-Is should remain first-choice treatment in these patients. Concerns have been raised, however, about whether an adequate dose of losartan was used and whether the therapy was initiated early enough to confer benefit.

Some of this uncertainty will be addressed in the ongoing Valsartan in acute myocardial infarction (VALIANT) trial, which is due to report in late 2003 (figure 4).[41] This study enrolled more than 14,500 post-MI patients with signs and/or symptoms of heart failure. The primary end point is all-cause mortality. Patients have been randomised to receive one of three treatments: valsartan 160 mg b.d. or captopril 50 mg t.d.s or valsartan 80 mg b.d. plus captopril 50 mg t.d.s. The results should help to clarify whether the optimal treatment after MI should be an ACE-I, an ARB or a combination of the two.

Heart failure

Inhibiting the RAS is beneficial in the treatment of heart failure. Treatment with both ACE-Is and beta blockers has been shown to improve outcomes in patients with heart failure and, together with loop diuretics, is currently recommended as optimal treatment. A number of studies have been designed to assess the efficacy of ARBs in ventricular dysfunction. The Evaluation of Losartan In The Elderly (ELITE) study investigated the changes in renal impairment in patients with heart failure: however, the secondary end point of all-cause death was reduced by 46% (p=0.035) in patients treated with losartan 50 mg compared to captopril 50 mg t.d.s.[42] Subsequently the larger ELITE II study was designed to look specifically at all-cause mortality.[43] It showed that there was no significant difference between the losartan group and the captopril group, but that fewer patients discontinued therapy on the ARB.

Figure 5. Prescribing of antihypertensive drug classes in the UK between January 1999 and January 2003. Moving Annual Total (MAT) sales of units of different drug classes from wholesalers. (Bracket after drug class shows percentage increase in sales from January 1999)



Data from IMS Health BPI, January 2003.

The Valsartan Heart Failure (ValHeFT) trial tested the hypothesis that the treatment of heart failure patients on standard therapy would benefit from the addition of valsartan 160 mg b.d. compared to placebo.[44] Of the 5,010 patients 92% were already receiving ACE-I therapy and 35% were receiving a beta blocker. This study was powered to consider two primary end points. There was no difference between the groups with respect to all-cause mortality, but the composite end point of mortality and morbidity (death, cardiac arrest, hospitalisation for heart failure, intravenous inotropes or vasodilator use) was significantly reduced by 13% in the valsartan group (p=0.009). This result included a 27% reduction in hospitalisation for heart failure (p<0.001). The mean change in ejection fraction, changes in New York Heart Association (NYHA) class and symptoms were also in favour of valsartan treatment.

Subsequent subgroup analysis suggested that initial background therapy influenced the response to valsartan, and one unexpected finding was an adverse effect on mortality and a trend towards an increase in morbidity with valsartan in patients who were receiving both an ACE-I and a beta blocker at randomisation. In patients receiving neither ACE-I nor beta blocker, valsartan significantly reduced mortality and morbidity during the study. As a consequence of this study, the FDA has issued a licence for its use in ACE-I-intolerant patients in the US. However, ARBs are not currently licensed for use in heart failure in the UK.

The ongoing Candesartan in Heart failure: Assessment of

Key messages

- ARBs are effective agents in reducing blood pressure
- ARBs have a placebo-like side-effect profile
- A number of recent trials have demonstrated the benefit of ARBs in hypertensive patients with diabetes
- RAS-blocking drugs appear effective in regressing left ventricular hypertrophy
- The British Hypertensive Society recommends ARBs as first-line agents in patients under 55, and as second-line agents in patients over 55

Reduction in Mortality and morbidity (CHARM) study is also investigating the effects of AT_1 receptor blockers in heart failure.[45] This study will compare the effects of candesartan and placebo on mortality and hospitalisation in three distinct patient groups. The groups are: patients with heart failure intolerant of ACE-Is, those already taking an ACE-I, and those with preserved systolic function. The results of this trial, expected in mid 2003, should clarify the place of angiotensin receptor blockers in the treatment of heart failure.

Current UK prescribing

The UK sales of the major classes of antihypertensive drugs over the last four years are illustrated in figure 5. There has been an 82% growth in the total sales of all the major drug classes, but the greatest percentage increases in sales have been for diuretics and ARBs. Some of the increase generally, and specifically for diuretics, may be due to the BHS guidelines published in September 1999 that recommended thiazides as first-line treatment. ARBs have seen a steady increase in absolute terms, but a large percentage increase in sales, probably as a consequence of emerging outcome trial evidence for the class (figure 5). ARBs will tend to be used in younger patients who cannot tolerate ACE-Is because of cough.

Summary and conclusions

The ARBs are a valuable addition to the classes of antihypertensive drugs available for the management of hypertension. They have comparable efficacy to other drug classes, and are usually very well tolerated. In elderly subjects the recent trials and British Hypertension Society recommendations support the use of thiazides or calcium channel blockers as first-line treatment. For younger patients, however, drugs that work on the renin-angiotensin system are preferred. Beta blockers are currently out of favour because of recent poor outcome data that include an increased incidence of the development of diabetes mellitus. ACE inhibitors and ARBs are therefore preferred as first-line treatment in younger patients with hypertension, as these patients are likely to have high renin levels and will generally respond well to these drug classes. Combinations of drugs should be used logically to enhance the likelihood of blood pressure control for patients.

ARBs are likely to be used in a high percentage of young patients because they do not cause the cough associated with ACE inhibition. ARBs will also be used for patients with co-morbid conditions such as diabetes, left ventricular hypertrophy and heart failure. The choice of ARB is likely to be a matter for individual drug formulary committees, which should consider all of the evidence available for individual drugs.

References

1. Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ; Comparative Risk Assessment Collaborating Group. Selected major risk factors and global and regional burden of disease. *Lancet* 2002;**360**: 1347-60.
2. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk patients randomised to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;**288**:2981-97.
3. Wing LM, Reid CM, Ryan P *et al*, for the Second Australian National Blood Pressure Study Group. A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med* 2003;**348**:583-92.
4. Neaton JD, Grimm RH Jr, Prineas RJ *et al*. Treatment of mild hypertension. Final results. *JAMA* 1993;**270**:713-24.
5. Materson BJ, Reda DJ, Cushman WC *et al*. Single drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. *N Engl J Med* 1993;**328**:914-21.
6. Conlin PR, Spence JD, Williams B *et al*. Angiotensin II antagonists for hypertension: Are there differences in efficacy? *Am J Hypertens* 2000;**13**: 118-26.
7. Fogari R, Mugellini A, Zoppi A *et al*. A double blind crossover study of the antihypertensive efficacy of angiotensin II receptor antagonists and their activation of the renin-angiotensin system. *Curr Ther Res* 2000;**61**: 669-79.
8. Lip GY, Beevers M, Beevers DG. The "Birmingham Hypertension Square" for the optimum choice of add-in drugs in the management of resistant hypertension. *J Hum Hypertens* 1998;**12**:761-3.
9. Dickerson JE, Hingorani AD, Ashby MJ, Palmer CR, Brown MJ. Optimisation of antihypertensive treatment by crossover rotation of four major classes. *Lancet* 1999;**353**:2008-13.
10. MacKenzie IS, Brown MJ. Genetic profiling versus drug rotation in the optimisation of antihypertensive treatment. *Clin Med JRCPL* 2002;**2**:465-73.
11. Brown MJ, Cruickshank JK, Dominiczak AF *et al*. Better blood pressure control: how to combine drugs. *J Hum Hypertens* 2003;**17**:81-6.
12. Dahlof B, Devereux RB, Kjeldsen SE *et al*. Cardiovascular morbidity and mortality in the losartan intervention for endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359**:995-1003.
13. Markham A, Goa KL. Valsartan: a review of its pharmacology and therapeutic use in essential hypertension. *Drugs* 1997;**54**:299-311.
14. Gillis JC, Markham A. Irbesartan: a review of its pharmacology and pharmacokinetic properties and therapeutic use in the management of hypertension. *Drugs* 1997;**54**:885-902.
15. Goldberg AI, Dunlay MC, Sweet CS. Safety and tolerability of losartan potassium, an angiotensin II receptor antagonist, compared with hydrochlorothiazide, atenolol, felodipine ER and ACE-inhibitors for the treatment of systemic hypertension. *Am J Cardiol* 1995;**75**:793-5.
16. Bloom B. Continuation of initial antihypertensive medication after 1 year of therapy. *Clin Ther* 1998;**20**:671-81.
17. Jones JK, Gorkin L, Lian JF, Staffa JA, Fletcher AP. Discontinuation of and changes in treatment after start of new courses of antihypertensive drugs: a study of a United Kingdom population. *BMJ* 1995;**311**:293-5.

18. Wogen J, Kreilick CA, Livornese R, Frech F. A population-based study of compliance and persistency with cardiovascular agents used in hypertension management. *Am J Hypertens* 2001;**14**(4, 2):112A.
19. Lithell H, Hansson L, Skoog I *et al*., for the SCOPE Study Group. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomised double-blind intervention trial. *J Hypertens* 2003;**21**:875-86.
20. Kjeldsen SE, Julius S, Brunner H *et al*. Characteristics of 15314 hypetensive patients at high coronary risk. The VALUE trial. *Blood Press* 2001;**10**:83-91.
21. Yeo WW, Rowland Yeo K. Predicting CHD risk in patients with diabetes. *Diabetic Med* 2001;**18**:341-4.
22. Rowland Yeo K, Yeo WW. Lipid lowering in patients with diabetes mellitus: what coronary heart disease risk threshold should be used? *Heart* 2002:**87**:423-7.
23. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD, for the Collaborative Study Group. The effect of angiotensin-converting enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993;**329**:1456-62.
24. Viberti G, Mogensen CE, Groop LC, Pauls JF, for the European Microalbuminuria Captopril Study Group. Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria. *JAMA* 1994;**271**:275-9.
25. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *BMJ* 1998;**317**:713-20.
26. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;**342**:145-153.
27. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE and MICRO-HOPE substudy. *Lancet* 2000;**355**:253-9.
28. Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P; Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001;**345**:870-8.
29. Viberti G, Wheeldon NM; MicroAlbuminuria Reduction With VALsartan (MARVAL) Study Investigators. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus. *Circulation* 2002;**106**:672-8.
30. Brenner BM, Cooper ME, de Zeeuw D *et al*., for the RENAAL Study Investigators. Effect of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;**345**:861-9.
31. Lewis EJ, Hunsicker LG, Clarke WR *et al*. Renoprotective effects of the angiotensin-receptor blocker irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;**345**:851-60.
32. Opie LH. Renoprotection by angiotensin-receptor blockers and ACE inhibitors in hypertension. *Lancet* 2001;**358**:1829-31.
33. Savage DD, Drayer JI, Henry WL *et al*. Echocardiographic assessment of cardiac anatomy and function in hypertensive subjects. *Circulation* 1979;**59**:623-32.
34. Devereux RB, Casale PN, Hammond IW *et al*. Echocardiographic detection of pressure-overload left ventricular hypertrophy. *J Clin Hypertens* 1987;**3**:66-78.
35. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990;**322**:1561-6.
36. Schmieder RE, Martus P, Klingbeil A. Reversal of left ventricular hypertrophy in essential hypertension. *JAMA* 1996;**275**:1507-13.
37. Malmqvist K, Kahan T, Edner M *et al*. Regression of left ventricular hypertrophy in human hypertension with irbesartan. *J Hypertens* 2001; **19**:1167-75.
38. Thurmann PA, Kenedi P, Schmidt A, Harder S, Rietbrock N. Influence of the angiotensin II antagonist valsartan on left ventricular hypertrophy in patients with essential hypertension. *Circulation* 1998;**98**:2037-42.
39. Nalbantgil S, Yilmaz H, Gurun G, Ozerkan F, Nalbantgil I, Onder R. Effects of valsartan and enalapril on regression of left ventricular hypertrophy in patients with mild to moderate hypertension: a randomised double-blind study. *Curr Ther Res* 2000;**61**:331-8.
40. Dickstein K, Kjekshus J; OPTIMAAL Steering Committee of the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. *Lancet* 2002;**360**:752-60.
41. Pfeffer MA, McMurray J, Leizorovicz A *et al*. Valsartan in acute myocardial infarction trial (VALIANT): Rationale and design. *Am Heart J* 2000; **140**:727-34.
42. Pitt B, Segal R, Martinez FA *et al*. Randomised trial of losartan versus captopril in patients over 65 with heart failure (ELITE). *Lancet* 1997;**349**:747-52.
43. Pitt B, Poole-Wilson PA, Segal R *et al*. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial (ELITE II). *Lancet* 2000;**355**:1582-7.
44. Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A randomised trial of the angiotensin receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;**345**:1667-75.
45. Swedberg K, Pfeffer M, Granger C *et al*. Candesartan in heart failure - assessment of reduction in mortality and morbidity (CHARM): rationale and design. *J Card Fail* 1999;**5**:276-82.

Introduction of valsartan into the 'Preferred Prescribing Practice' list for Wokingham PCT

MAHA YASSAIE

Abstract

A Preferred Prescribing Practice (PPP) list includes drugs that have rigorous safety profiles, and are effective, economic and acceptable to the patient. This article explains the decision-making process for inclusion of valsartan in the PPP for Wokingham primary care trust (PCT).

Within the angiotensin receptor blockers class, valsartan is supported by significant clinical data for its use in essential hypertension. It has been demonstrated that valsartan produces effective blood pressure reduction for over 24 hours, that dose titration gives greater efficacy and that tolerance does not develop with long-term usage. Valsartan has a side-effect profile comparable to placebo and is tolerated well by patients.

This evidence has qualified valsartan to be included in Wokingham PCT's PPP list.

Key words: preferred prescribing practice, angiotensin receptor blocker, valsartan, hypertension.

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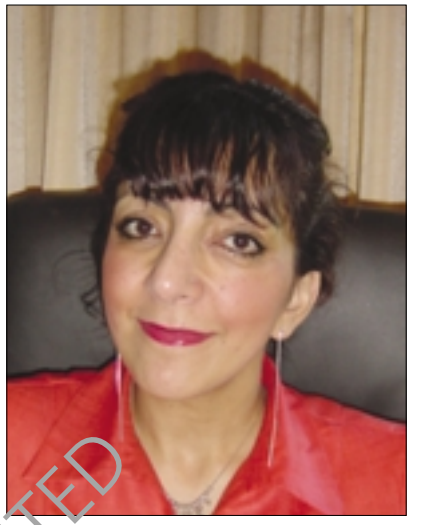

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Introduction

There are three principal reasons why a primary care trust (PCT) needs a Preferred Prescribing Practice (PPP):

- It is a step towards ensuring that patients are consistently receiving the best care that medical knowledge can offer.
- The preferred drug list encourages the prescribing of drugs which are safe, effective, economic, appropriate to the patient's condition and acceptable to patients.[2]
- The rationale for developing such a preferred drug list is that by selecting a few of the many drugs available doctors are protected from information overload and patients are protected from accidental misuse.[3]

The National Service Frameworks on Coronary Heart Disease and Diabetes have highlighted the need to control blood pressure (BP). There are many agents on the market for treating hypertension. However, to be able to improve the quality of care provided for patients, Primary Care Organisations (PCOs) are concentrating increasingly on appropriate, effective, affordable and evidence-based prescribing. To achieve these goals only drugs which have been under extensive evaluation would be included in the PPP list.

The purpose of this article is not to recommend when patients should be on angiotensin receptor blockers (ARBs) but to explain why valsartan is one of the ARBs of choice for the PPP of Wokingham PCT. The National Institute for Clinical Excellence (NICE) has yet to pronounce on the role of these agents and few official bodies (such as the World Health Organisation and the International Society for Hypertension), have made recommendations on the role of ARBs in the management of hypertension.

ARBs for the treatment of high blood pressure

Pharmacology

Drugs that act on the renin-angiotensin-aldosterone system (RAS) represent a significant therapeutic development in the management of cardiovascular disease. There are two classes of drugs that act directly on this system, the angiotensin-converting enzyme (ACE) inhibitors and the ARBs. Both classes of drugs produce a comparable reduction in systolic and diastolic BP in hypertensive populations; however, tolerability and adverse reactions differ between these classes.

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Table 1. Clinical qualities of valsartan

Clinical experience	Effective BP control		Effective hypertension risk factor management	Placebo-like tolerability
	Monotherapy	Combination therapy		
More than 30,000 patients in hypertension studies	✓	✓	LVH	✓
Extensive ongoing outcome trial programme			Microalbuminuria	

Key: BP = blood pressure; LVH = left ventricular hypertrophy

The ARBs (sartans) are non-peptide imidazole derivatives that block the effects of angiotensin II by acting as antagonists at the AT_1-receptor, with varying levels of surmountability. ARBs do not inhibit the synthesis of angiotensin II: in fact, selective blockade of the AT_1-receptor subtype leads to a reflex increase in levels of circulating angiotensin II. ACE inhibitors (ACE-Is) block the breakdown of bradykinin, which is believed to be the mechanism for the cough observed with these drugs. By contrast, ARBs do not inhibit bradykinin degradation. Furthermore, as ARBs bind at the receptor for angiotensin II they can block the action of angiotensin II generated through non-ACE pathways.

The importance of complete blockade of the RAS and of selective AT_1-receptor blockade are expected to determine how ARBs fare in the major ARB outcome studies. In turn this will define the role of ARBs and whether they will supersede ACE-Is or be used as adjuvant therapy.

Efficacy

ACE-Is are firmly established in the management of hypertension but also for heart failure, post-myocardial infarction (MI) and in type 1 diabetes. Data are also emerging to support their use in type 2 diabetes. ARBs are effective at reducing BP: many studies have shown them to be as effective as the other major classes of antihypertensive drugs,[4-8] with tolerability superior to many agents.[9]

A meta-analysis of 43 published randomised controlled trials evaluating the efficacy of four out of six agents available, suggests that the average BP reduction with the ARB class is 13/10 mmHg.[10]

Possible advantages of ARBs in comparison to ACE-Is are: less first-dose hypotension; less renal dysfunction; reduced cough; and increased compliance. Although ACE-I intolerance is not a licensed indication for initiating an ARB, it is currently the most common reason for doing so.

Evaluating valsartan for inclusion in the PPP

Pharmacokinetics

Valsartan is administered orally and is well absorbed, with a bioavailability of 23%. The peak plasma concentration is reached after 2–4 hours. Valsartan is only minimally metabolised, with more than 80% excreted unchanged. The cytochrome P450 system is not thought to be involved in its metabolism. The half-life for valsartan is nine hours, with about 30% being eliminated via the kidneys.

The dose of valsartan should be reduced in patients with moderate/severe renal impairment, mild/moderate hepatic impairment and in patients over 75 years old.

Valsartan was developed during the 1990s and first made available in the UK in 1997. There is a considerable amount of supporting data from large clinical trials and from several patient-years of treatment. Valsartan is licensed for the treatment of essential hypertension as monotherapy or in combination with other antihypertensive drugs.[11]

Use in hypertension

When used as monotherapy, valsartan is effective at reducing BP in hypertensive patients.[12,13] Many controlled studies have confirmed this and shown valsartan to be at least as effective as the other major classes of antihypertensives (diuretics, calcium channel blockers, ACE-Is and beta blockers). Valsartan 80 mg has been shown to reduce BP by up to 16/13 mmHg.

Increased efficacy is gained by titrating from the usual starting dose of valsartan 80 mg to 160 mg.

Valsartan is also effective when used in combination with other antihypertensive agents.[14] When added to bendrofluazide, valsartan has been shown to produce an additional 15/9 mmHg reduction in BP. When used in combination with amlodipine 5 mg, valsartan 80 mg has been shown to produce a 16/13 mmHg reduction in BP in treatment-resistant hypertensive patients.

Valsartan is administered once a day. It effectively reduces BP for 24 hours and there is evidence to suggest that it works for up to 32 hours.

Trials have followed patients treated with valsartan for more than three years. These studies have confirmed that tolerance to this drug does not develop and that a high level of compliance is maintained.

In a study of patients with hypertension and left ventricular hypertrophy (LVH), valsartan 80 mg once daily reduced LVH by 20%, and to a similar degree to patients treated with enalapril 20 mg.

Microalbuminuria was reduced by 47% in hypertensive patients with type 2 diabetes and microalbuminuria who were

Key messages

- A preferred drug list encourages the prescribing of safe, effective and appropriate drugs
- Drugs that act on the renin-angiotensin system are a significant development in the management of cardiovascular disease
- There are several potential advantages of ARBs in comparison with ACE-Is
- There is a good evidence base to support the use of valsartan in hypertension

treated with valsartan, compared to a 11% reduction in patients treated to a similar BP with amlodipine.

Clinical trials have confirmed that the side-effect profile of valsartan is similar to that of placebo; increasing the dose from 80 to 160 mg does not increase the frequency of side effects significantly.

In a large controlled trial in patients with heart failure, patients receiving valsartan 160 mg twice daily in addition to standard therapy experienced a significant reduction in morbidity and mortality of 13%. In patients not receiving an ACE-I as part of their standard therapy, there was a 33% reduction in mortality with valsartan treatment. Valsartan is not licensed at present for the treatment of heart failure.

Safety

Risk management evaluation reflects both qualitative and quantitative data from longitudinal studies and Committee on Safety of Medicines (CSM) black triangle status (via the yellow card scheme). From the data available at the present time, valsartan has no clinically significant interaction with other medication. Valsartan does not have black triangle status.[15]

Cost

Valsartan is competitively priced in the ARB class: the cost of 28 days' treatment is £15.75 for 80 mg and £19.69 for 160 mg.[16]

Conclusion

Valsartan is supported by significant clinical data for its use in essential hypertension. It produces effective BP reduction for over 24 hours, it can be titrated for greater effect, and tolerance does not develop with long-term usage. Valsartan has a side-effect profile comparable to placebo and is tolerated well by patients.[17]

This evidence has qualified valsartan to be included in Wokingham PCT's Preferred Prescribing Practice list.

References

1. Bradley CP, Blenkinsopp A. Responding to changing healthcare system, adapting prescribing in the new NHS: prescribing in primary care. *MIMS Magazines* 1996;**42**:141-62.
2. Bradey CP. Advisor suggests a DIY approach. *MIMS Magazines* 1990;**15**: 47-50.
3. Parish PA. Drug prescribing; the concern of all. *J Roy Soc Health* 1973; **93**:213-17.
4. Weber MA, Bynny RL, Pratt JH *et al*. Blood pressure effects of the angiotensin II receptor blocker, losartan. *Arch Intern Med* 1995: **155**:405-11.
5. Pitt B, Poole-Wilson PA, Segal R *et al*. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial. Losartan Heart Failure Survival Study, ELITE II. *Lancet* 2000; **355**:1582-7.
6. Dahlof B, Devereux RB, Julius S *et al*, for the LIFE Study Group. Characteristics of 9194 patients with left ventricular hypertrophy. *Hypertens* 1998;**3**:989-97.
7. Dickstein K, Kjekshus J, for the OPTIMAAL Study Group. Comparison of the effects of losartan and captopril on mortality in patients after acute myocardial infarction; the OPTIMAAL trial design. *Am J Cardiol* 1999;**83**:477-81.
8. Viberti G, Wheeldon NM. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus. *JAMA* 2002;**106**:672-8.
9. Mann J, Julius S. The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial of cardiovascular events in hypertension. Rationale and design. *Blood Press* 1998;**7**:176-83.
10. Colin PR. Angiotensin II antagonists for hypertension; are there differences in efficacy? *Am J Hypertens* 2000;**13**:418-26.
11. Anon. Therapeutic class summaries. Evaluated information for the NHS, Angiotensin 2 receptor antagonists. UK Medicine Information Pharmacist Group NHS (UKMI), December 2002.
12. Cohn JN, Tognoni G, Glazer RD. Rationale and design of the Valsartan Heart Failure Trial; a large, multinational trial to assess the effects of valsartan, an angiotensin-receptor blocker, on morbidity and mortality in chronic congestive heart failure. *J Cardiac Failure* 1995;**5**:155-60.
13. ValHeFT. Results presented at the 50th Scientific Sessions of the American College of Cardiology. Orlando, Florida, March 2001.
14. Omar Ali. Comparative review of angiotensin II–receptor antagonists. *Prescriber* 2001;(suppl):1-12.
15. British National Formulary, September 2002.
16. Monthly Index of Medical Specialities, March 2003.
17. Oparil S, Dyke S, Harris F *et al*. The efficacy and safety of valsartan compared with placebo in the treatment of patients with essential hypertension. *Clin Ther* 1996;**18**;797-810.