Evidence-based treatment of hypertension: what's the role of angiotensin II receptor blockers?

In this article the authors look at trials of angiotensin II receptor blockers in hypertension, heart failure and diabetes with a primary care perspective.

Abstract

Many large studies have confirmed the importance of controlling hypertension in reducing cardiovascular morbidity and mortality. Prescribers are now faced with a wide choice of antihypertensives and a growing body of evidence about their effects.

This article reviews recent evidence about angiotensin II receptor blockers (ARBs). It concludes that they are effective in reducing blood pressure and cardiovascular disease. ARBs also have a renoprotective effect in diabetes. They are generally better tolerated than ACE inhibitors or beta blockers. Newer members of the class may be more effective than older ones at controlling hypertension, and combinations of ARBs with ACE inhibitors may be more effective than either drug alone. Many patients will require combinations of different classes of antihypertensive agents, and ARBs have an important place in providing therapy tailored to the needs of the individual patient.

Key words: hypertension, antihypertensive agents, angiotensin receptors, renin-angiotensin system.

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Introduction

High blood pressure is one of the three most important risk factors for cardiovascular disease[1] and is a major burden for global health.[2] In the UK, about 40% of people aged 35–64 years are hypertensive (i.e. have a blood pressure above 140/90 mmHg).[3] Each year around 212,000 people in the UK die from cardiovascular disease and, of these, nearly 60,000 deaths are due to stroke (figures for 2001).[4] In recent years, the relative frequency of stroke has been increasing compared with coronary heart disease, and the primary goal of antihypertensive therapy is now the prevention of stroke.[5]

Although hypertension responds well to treatment, only 10–30% of hypertensive patients in the UK have their blood pressure controlled[3,6] and suboptimal blood pressure control may account for 62,000 unnecessary deaths per year.[1] Theoretical models of the effects of poor blood pressure control have been confirmed by a study in general practice, which showed that the risk of stroke was related to the quality of blood pressure control, and that inadequate control may account for about 21% of strokes.[7]

> ***'Blood pressure control in patients with diabetes is particularly important'***

Prescribers are faced with many data from an expanding pool of large studies, yet, beyond the sheer time needed to update the evidence base, it can be difficult to translate and synthesise results into rational treatment decisions for individual patients.[8,9]

One important factor affecting the application of clinical trial evidence into routine practice is the range of study designs. Most new treatments are licensed on the basis of relatively small studies conducted over fairly short timeframes in tightly controlled populations. These studies are designed to demonstrate the efficacy of the drug either against placebo or current best treatment. Efficacy is usually expressed in terms of the treatments' effects on mean blood pressure, expressed in mmHg. Such outcomes are easily quantified and such study designs limit the number of patients who are exposed to the new treatment. These patients will be carefully selected, and those with complicating factors such as other illnesses or those receiving other medication are usually excluded. These studies produce simple and unequivocal results, but they may not be applicable to the broader patient population.

Furthermore, a fall in blood pressure is only a surrogate end point. The real reason for treating hypertension is to reduce the risk of cardiovascular disease. Much larger and longer studies are needed to measure end points such as the incidence of stroke or the death rate from cardiovascular disease. Not only are such studies difficult (and costly) to perform, but their results are often harder to interpret. This is because, in long-term studies, a significant proportion of patients will stop taking the study treatment, many patients require more than one antihypertensive agent and other factors may change over time. For example, the proportion of patients in hypertension treatment trials also receiving statins

has increased considerably over the past five years and this independently influences cardiovascular morbidity and mortality. Other risk factors, such as patients' concurrent diseases, may also vary unpredictably over the course of the study.

Because these large-scale effectiveness studies are so expensive to organise, and take such a long time to generate meaningful data, they have not been performed for every member of every class of antihypertensive agent, let alone for the enormous number of possible treatment combinations. Results of single studies may therefore fail to provide answers about individual treatment decisions. Doctors have to decide whether results of studies are applicable to other members of the same class of drug to different combinations or to different patient populations.

The newest class of antihypertensive agents is the angiotensin II receptor blockers (ARBs). This article reviews recent evidence on ARBs, with the aim of helping prescribers make rational decisions when selecting antihypertensive therapy for their patients.

The angiotensin II receptor blockers (ARBs)

Angiotensin II is formed from the conversion of angiotensinogen to angiotensin I. This is converted, in turn, to angiotensin II by angiotensin converting enzyme (ACE). Angiotensin II is a potent vasoconstrictor and also stimulates the release of aldosterone, which causes a further rise in blood pressure.[10] ARBs block the effects of angiotensin but, unlike ACE inhibitors, do not inhibit the breakdown of bradykinin or other kinins which are assumed to cause unwanted effects such as the dry cough that affects some patients taking ACE inhibitors.

Members of the ARB class licensed for use in the UK include candesartan (Amias®), eprosartan (Teveten®), irbesartan (Aprovel®), losartan (Cozaar®), olmesartan (Olmetec®), telmisartan (Micardis®) and valsartan (Diovan®). They are sometimes referred to as the 'sartans'.

Efficacy of ARB monotherapy in reducing blood pressure and cardiovascular end points

The LIFE (Losartan Intervention For Endpoint reduction) trial,[11] studied 9,193 patients aged 55–80 years with primary hypertension from the UK, Scandinavia and the US. Patients were excluded if they had had a stroke or myocardial infarction (MI) within the previous six months. Participants were randomised to receive either an ARB (losartan) or a beta blocker (atenolol) for at least four years.

Both treatments had similar effects on mean blood pressure (which fell by 30.2/16.6 mmHg in the losartan group and 29.1/16.8 mmHg in the atenolol group). However, the ARB was more effective at reducing stroke and left ventricular hypertrophy (LVH) than atenolol (relative risk 0.87 (p=0.021) for composite end point of death, MI or stroke). A post-hoc analysis also indicated that losartan provided greater protection than atenolol against sudden cardiac death in patients with diabetes (hazard ratio 0.49, p=0.027).[12] Losartan was better tolerated than atenolol: significantly fewer patients stopped treatment as a result of adverse events and there were fewer serious adverse events in the ARB group.

> ***'Suboptimal blood pressure control may account for 62,000 unnecessary deaths per year'***

The OPTIMAAL (Optimal Trial In Myocardial Infarction with the Angiotensin Receptor Blocker Losartan) study compared losartan with the ACE inhibitor captopril,[13] recruiting 5,477 European patients aged over 50 with confirmed acute MI and heart failure. There was no significant difference in overall mortality between the groups. The ARB was better tolerated than the ACE inhibitor, with significantly fewer withdrawals due to adverse effects.

Losartan was the first ARB to be licensed and is therefore the most studied. There is evidence that, despite some similarities, the ARBs may vary in their effects. For example, small studies have shown that the newer generation ARBs, when titrated to optimal doses, are significantly more effective than losartan at reducing blood pressure in patients with mild-to-moderate hypertension.[14,15] One study of 588 patients with diastolic blood pressure (DBP) of 100–115 mmHg and mean daytime DBP of 90–120 mmHg compared 20 mg olmesartan with 50 mg losartan, 80 mg valsartan or 150 mg irbesartan. Olmesartan and irbesartan produced significantly greater mean decreases in blood pressure after eight weeks than losartan or valsartan.[16] Detailed findings are shown in table 1.

Another eight-week study of 332 patients found that candesartan was more effective than losartan (in terms of the percentage of responders and the mean decrease in blood pressure).[17]

The CHARM (Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity) study compared candesartan with placebo in 7,601 patients with chronic heart failure (CHF) and followed them for at least two years. Candesartan significantly reduced the primary outcome of cardiovascular deaths (hazard ratio 0.87, p=0.006) and hospital admissions for heart failure (20% candesartan *vs.* 24% placebo, p<0.001).[18] The CHARM-Alternative study enrolled 2,028 patients with CHF who were intolerant of ACE inhibitors. In this group the hazard ratio for candesartan was 0.70 (p<0.001) for cardiovascular death or hospital admission for CHF.[19] The CHARM-Preserved trial considered 3,023 patients with CHF and preserved left ventricular ejection fraction: it showed a hazard ratio of 0.89 for the primary outcome (p=0.051) but no difference in cardiovascular deaths between the candesartan and placebo groups.[20] A pooled analysis across all three CHARM studies showed a signifi-

Table 1. Differences between four 'sartans' in patients with essential hypertension (n=588 with DBP 100–115 mmHg) shown by changes from baseline blood pressure values after eight weeks' treatment (all expressed in mmHg) (data from Oparil 2001[16])

Change from baseline in:	Olmesartan	Irbesartan	Losartan	Valsartan
Sitting cuff DBP	11.5**	9.9	8.2	7.9
Mean 24h DBP	8.5*	7.4	6.2	5.6
Mean 24h SBP	12.5*	11.3	9.0	8.1

** Significantly greater reduction than irbesartan, losartan or valsartan (p<0.05)
* Significantly greater reduction than losartan or valsartan (p<0.05)
Key: DBP = diastolic blood pressure; SBP = systolic blood pressure

cant benefit in reduction of overall mortality (23% for candesartan *vs.* 25% for placebo, hazard ratio 0.9, p=0.032).

Renal protection in diabetes

Blood pressure control in people with diabetes is particularly important, since hypertension is the second commonest cause of renal failure. Several large-scale studies have shown that ARBs are effective in protecting against the progression of nephropathy due to type 2 diabetes. The RENAAL (Reduction of Endpoints in NIDDM with the ARB Losartan) study recruited 1,513 hypertensive patients with type 2 diabetes and nephropathy and followed them for over three years.[21] They were randomised to receive either losartan or placebo in addition to 'conventional' antihypertensives such as beta blockers. Losartan reduced the occurrence of proteinuria, doubling of serum creatinine concentration and end-stage renal disease by 35%, 25% and 28% respectively (p<0.01 in all cases). This led to a 16% risk reduction for the composite end point (p=0.02). The authors noted that 'the benefit exceeded that attributable to changes in blood pressure'.

IDNT (the Irbesartan Diabetic Nephropathy Trial) randomised 1,715 patients with hypertension and nephropathy due to type 2 diabetes to receive irbesartan, amlodipine or placebo.[22] The risk of a doubling of serum creatinine was 33% lower in the irbesartan group than in the placebo group and 37% lower than in the amlodipine group (p<0.01 in both cases). The risk of end-stage renal disease was reduced by 23% (p=0.07). Again, the investigators commented that the protection afforded by the ARB appeared to be independent of the reduction in blood pressure. The IRMAII study showed similar effects.[23] The hazard ratios for developing overt nephropathy (defined as urinary albumin excretion > 200 mcg/min and at least 30% higher than baseline) were 0.56 for 150 mg irbesartan (p=0.05) and 0.32 for 300 mg irbesartan (p<0.001) compared with placebo.

ARBs in combination therapy

Perhaps because of the complex pathophysiology underlying hypertension, many patients obtain better control of blood pressure with a combination of antihypertensives than with monotherapy. For example, in the HOT study of 18,790 patients, which controlled blood pressure to a number of prespecified targets, 41% of participants required an ACE inhibitor and 28% received a beta blocker in addition to felodipine.[24] In the UKPDS (United Kingdom Prospective Diabetes Study) study of people with type 2 diabetes, about 60% of participants required more than one antihypertensive drug to achieve the target blood pressure and about 30% required three or more agents.[25] Combined regimens may also permit drugs to be used at lower doses than for monotherapy, which may improve their tolerability.

'ARBs are generally very well tolerated'

The most recent British guidelines on hypertension treatment acknowledge that 'most people will require more than one drug to control blood pressure.'[26] However, an accompanying editorial notes that 'a common reason for poor control of blood pressure is that most doctors keep using monotherapy in patients who obviously need combination therapy to normalise blood pressure.'[3]

The CALM (Candesartan and Lisinopril in Microalbuminuria) study found that candesartan was as effective as the ACE inhibitor lisinopril in reducing microalbuminuria in hypertensive patients with type 2 diabetes, but combined treatment was even better, achieving a 50% reduction in albumin:creatinine ratio compared with 24% for candesartan alone and 39% for lisinopril alone.[27] The combination was well tolerated.

The CHARM-Added trial showed that the addition of candesartan to an ACE inhibitor significantly reduced cardiovascular deaths and unplanned hospital admissions (the composite primary outcome) in 2,548 patients with chronic heart failure.[28] In this study, patients were randomised to receive either candesartan or placebo in addition to their current ACE inhibitor (the most widely used being enalapril, lisinopril, captopril and ramipril). Over a median follow-up of 41 months, 38% of patients in the ACE inhibitor plus candesartan group and 42% in the ACE inhibitor plus placebo group experienced the primary outcome (hazard ratio 0.85, p=0.011). The authors concluded that adding candesartan to ACE inhibitor treatment 'leads to a further clinically important reduction in relevant cardiovascular events' and that the benefits of candesartan were similar in all subgroups, including patients receiving beta blockers at baseline.[28]

Another study has examined the effects of losartan plus trandolapril in Japanese patients with non-diabetic renal disease.[29] The COOPERATE (Combination Treatment of Angio-

tensin-II Receptor Blocker and Angiotensin-Converting Inhibitor in Non-Diabetic Renal Disease) study recruited 336 patients; of those receiving the combination of the ARB and the ACE inhibitor, only 11% reached the primary end point of doubling of serum creatinine or end-stage renal disease, compared with 23% in both the losartan and the trandolapril monotherapy groups (hazard ratios 0.38, p=0.018 and 0.4, p=0.016 respectively). The frequency of side-effects with combination treatment was the same as with trandolapril alone.

However, the triple combination of ARBs, ACE inhibitors and beta blockers may be less advantageous, at least for patients with chronic heart failure using valsartan, according to the findings of VAL-HeFT (the Valsartan Heart Failure Trial).[30] This study randomised 5,010 patients with NYHA class II-IV heart failure to either valsartan or placebo. Treatment with beta blockers was at the discretion of the physician. There was a significant decrease in mortality and morbidity from heart failure in the valsartan group, but the beneficial effects were not seen among patients who were receiving the triple combination of valsartan, an ACE inhibitor and a beta blocker. Since this was a post-hoc sub-group analysis, the apparent increase in morbidity in this group might have been due to other risk factors present in the patients who were already receiving both an ACE inhibitor and a beta blocker at baseline. The CHARM-Added trial found no difference between the 702 patients receiving a beta blocker and an ACE inhibitor plus candesartan with other predefined sub-groups regarding the benefits of adding candesartan.[28]

Recent prescribing guidelines for the NHS note that no ARBs are currently licensed for use in heart failure in the UK, and advise caution when combining them with an ACE inhibitor and a beta blocker.[31]

Tolerability of ARBs

ARBs are generally very well tolerated. Several large studies have shown that losartan is better tolerated than the ACE inhibitor captopril[13,32] or the beta blocker atenolol.[11] In the OPTIMAAL study (n=5,477), fewer patients receiving losartan than captopril stopped treatment because of an adverse event (7% *vs.* 14%, p<0.001). In the LIFE study of 9,193 hypertensive patients, withdrawals because of adverse events

Key messages

- The primary goal of antihypertensive therapy is now the prevention of stroke
- The benefit in patients with type 2 diabetes of ARB treatment exceeds that attributable to changes in blood pressure
- The ARBS are highly effective in lowering blood pressure and reducing cardiovascular mortality
- More recent ARBs may be more effective and better tolerated than earlier members of the class

'ARBs have an important place in the treatment of uncomplicated hypertension'

were around 13% in the losartan group and 18% in the atenolol group (p<0.001).[11] Although studies have suggested differences in efficacy between different ARBs there do not appear to be significant differences in tolerability among the class.[16] Olmesartan has been shown to have a similar adverse event profile to placebo in a number of studies.[33]

The tolerability of the ARBs sets them apart from the ACE inhibitors. The ELITE II study of 3,152 patients aged over 60 years with heart failure showed that patients taking losartan were significantly less likely to discontinue treatment because of adverse effects (10% losartan *vs.* 15% captopril, p<0.001),[32] and, in particular were significantly less likely to discontinue because of troublesome cough than those taking captopril (0.3 *vs.* 2.7%, p<0.001).[32] With an asymptomatic condition such as hypertension, long-term compliance can be a problem and side effects have been shown to lead to non-compliance, or to under-treatment with suboptimal doses.[34]

The CHARM-Alternative trial recruited 2,028 patients with chronic heart failure who were intolerant of ACE inhibitors.[19] The most common reasons for intolerance were cough (72%), hypotension (13%) and renal dysfunction (12%). Candesartan significantly reduced cardiovascular mortality and hospital admission in these patients (hazard ratio 0.7, p<0.001) and was generally well tolerated. Discontinuation rates were similar for the candesartan and placebo groups (30% and 29%, respectively).

Hypertensive patients tend to be elderly and often have other medical conditions. It is therefore important that long-term treatments such as antihypertensives, do not interact with other medications.[35]

Conclusions

Prescribers now have a wide choice of antihypertensive treatments. This is helpful, since treatment needs to be tailored for individual patients and the majority of patients will require multiple treatments. In the past five years or so, results from large-scale randomised studies have confirmed the importance of controlling blood pressure and the effectiveness of antihypertensive treatment in reducing cardiovascular mortality and morbidity in a range of patient populations. However, these large studies have also shown that patients usually require

combination therapy using more than one class of drug.

The ARBs are highly effective in lowering blood pressure and reducing cardiovascular mortality. They also appear to provide additional renal protection in patients with diabetes, and this effect is independent of their effect on blood pressure. Combinations of ARBs with drugs from other classes such as ACE inhibitors have been found to be highly effective; they may permit lower doses of ACE inhibitors to be used than in monotherapy, which may lower the incidence of dose-related adverse effects. The ARBs themselves are very well tolerated and are not associated with the side-effects known to cause compliance problems with beta blockers, ACE inhibitors and calcium channel blockers such as impotence, dry cough and peripheral oedema.

Although the older ARBs such as losartan have been studied most widely, there is growing evidence that more recent ARBs, such as candesartan and olmesartan, may be more effective and even better tolerated than the earlier members of the class. Some of these differences in observed efficacy may relate to duration of effect since the ARBs, as with most classes of antihypertensives, display differences in their ability to provide true 24-hour control of blood pressure. This is true even amongst once daily dosed treatments, and results in variable rates of 'hangover' therapeutic response in cases of late or missed doses.

The most recent guidelines from the British Hypertension Society state that ACE inhibitor intolerance, diabetic nephropathy, hypertension with left ventricular hypertrophy, and heart failure in ACE inhibitor-intolerant patients post-MI are all 'compelling indications' for the use of ARBs.[26] They also suggest that left ventricular dysfunction post-MI and intolerance of other antihypertensives are 'possible indications' for their use. Other 'possible indications' are proteinuric renal disease and chronic renal disease, although the guidelines note that renovascular disease is a contraindication and therefore recommend the use of ARBs in such patients only under specialist supervision.[26] ARBs have an important place in the treatment of uncomplicated hypertension as part of combination therapy and may be first-line treatment in patients with concomitant disease.

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Conflict of interest

FDRH, PI and JR have received sponsorship to scientific meetings and/or acted as advisory board members for pharmaceutical companies that market ARBs and other cardiovascular drugs.

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BOOK REVIEWS

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ancillary roles of the endothelin system. The chapters on angiogenesis, pulmonary fibrosis, proinflammatory mediators, the sympathetic nervous system and endothelin have enough information to introduce the reader to the critical issues in each area. A further chapter on endothelin in portal hypertension introduces this new arena.

The section on new therapeutic approaches offers an update on the status of the "dream list" of therapeutic targets, including cardiovascular manifestations of HIV infection, heart failure and systemic sclerosis. More research is necessary before a targeted strategy can be developed. A unique and practical chapter on the long-term and survival effects with endothelin receptor antagonism describes the comprehensive data regarding the role of the orally active, dual endothelin receptor antagonist bosentan in patients with pulmonary arterial hypertension.

This book is an ambitious effort to review the state-of-the-art knowledge about the endothelin system with many future perspectives. The chapters are narrative reviews, and the authors provide information about the most recent findings in a range of fields. This comprehensive reference will be invaluable to clinicians and researchers.

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Heart failure updates

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A wide array of texts are dedicated to heart failure but few provide a balanced overview of key areas of development or controversy, and many are outdated by the time of publication. The editors of this book, John McMurray and Marc Pfeffer, must be commended on producing a very informative and yet concise state-of-the-art text which covers a wide range of topics, written by world authorities.

The foreword by Eugene Braunwald highlights the magnitude of the current heart failure pandemic, which he describes as "the last battleground of heart disease". As a clinician's armamentarium grows, it is crucial to keep up-to-date with the evidence and rationale for novel therapies in the management of patients with chronic heart failure. It is pleasing to see the editors have included therapies that were perceived as attractive but which have been shown to be disappointing in clinical studies. Chapters are dedicated to vasopeptidase inhibitors (omapatrilat), endothelin antagonists and anti-tumour necrosis factor therapy.

Other chapters include the thorny discussion of diastolic heart failure, metabolic co-morbidities and utilisation of brain natriuretic peptide in clinical practice. Therapies that now form the bread and butter of drug treatment are discussed in turn. These chapters include valuable clinical recommendations and evidence to support the selection of one agent over another. Despite the obvious focus on conventional drug therapy for chronic heart failure, the book also includes evidence (or lack of it) behind therapies for acute decompensated heart failure. The final three chapters detail supporting nurse-led intervention, innovative surgery and devices (CRT and AICD).

The style throughout is readable and clinically orientated. A comprehensive reference list is provided for each chapter. Editorial notes at the end of relevant chapters detail 'late breaking clinical trials'. These are detailed and have ensured that the book was truly contemporary when it went to press. I believe that this book would be of great value to any healthcare professional involved in the management of patients with heart failure and is a must for the bookshelf of all cardiac departments.

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