Role of Angiotensin Receptor Blockers as Monotherapy in Reaching Blood Pressure Goals

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The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure emphasizes the urgent need to lower blood pressure (BP) to a goal of <140/90 mm Hg in patients with uncomplicated hypertension and to <130/80 mm Hg in high-risk patients, such as those with diabetes mellitus or chronic kidney disease, to prevent cardiovascular disease morbidity and mortality. Consequently, a meaningful measure of the efficacy of an antihypertensive therapy is its ability to achieve BP reduction to below the recommended BP goals.

Angiotensin II receptor blockers (ARB) are highly effective antihypertensive agents with excellent tolerability profiles similar to those of placebo. A literature search using MEDLINE, EMBASE, and BIOSIS to identify studies reporting data on the percentage of patients attaining BP goals found that monotherapy with an ARB can generally result in the attainment of the diastolic BP (DBP) goal of <90 mm Hg in approximately 50% of hypertensive patients. However, to our knowledge, the attainment of the systolic BP (SBP) and combined SBP/DBP goals with ARB monotherapy has not been reported. Therefore, a secondary analysis of BP efficacy data from a published study that directly compared recommended starting doses of four currently marketed ARB was performed to assess combined SBP and DBP goal attainment. This analysis showed that the percentage of patients achieving the combined SBP/DBP goal rate of <140/90 mm Hg was highest with olmesartan medoxomil (32.4%) compared with recommended starting doses of losartan potassium (16.1%), valsartan (14.5%), or irbesartan (25.9%).

Optimal ARB monotherapy can achieve recommended BP goals in a significant proportion of hypertensive patients. However, the majority of hypertensive patients will require combination therapy with two or more antihypertensive agents. Am J Hypertens 2005;18:287–294 © 2005 American Journal of Hypertension, Ltd.

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Hypertension, defined as a systolic blood pressure (SBP) ≥140 mm Hg and/or a diastolic blood pressure (DBP) ≥90 mm Hg, currently affects approximately 50 million individuals in the United States.1 In 1999 to 2000, it was estimated that 32% of the US population age ≥20 years and 71% of men and 85% of women age ≥75 years had hypertension.2 The prevalence of hypertension appears to be increasing. The National Health and Nutrition Examination Survey (NHANES), conducted in 1999 to 2000 by the National Center for Health Statistics, indicated that 28.7% of surveyed individuals (age ≥18 years) had hypertension, an increase of 3.7% over the previous NHANES III survey conducted from 1988 to 1991 (phase 1).3 Only 69% of hypertensive individuals in the most recent NHANES survey were aware of their hypertension, and only 58% of those were receiving treatment.1,3

Chronically elevated blood pressure (BP) is associated with an increased risk of cardiovascular morbidity and mortality, as well as with end-stage renal disease.5,4 Effective control of BP significantly reduces the risk of stroke, coronary heart disease, heart failure, and chronic kidney disease.1,4–6 Data from clinical trials indicate that antihypertensive therapy reduces the incidence of stroke by 35% to 40%, myocardial infarction by 20% to 25%, and heart failure by >50%.1,7


As highlighted in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7 Report),1 BP is not being adequately controlled in the US. In the NHANES 1999 to 2000 survey, BP was controlled


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(<140/90 mm Hg) in only 31% of hypertensive individuals age ≥18 years, representing BP goal attainment in just more than one half of those patients treated. Although this is an improvement over previous surveys, it is still far from ideal.\textsuperscript{1,3}

There is a continuous log-linear relationship between levels of SBP and DBP and cardiovascular risk, independent of other risk factors.\textsuperscript{1,4,6} throughout the usual BP range down to at least a level of 115 mm Hg SBP and 75 mm Hg DBP. An increase in usual SBP of 20 mm Hg or in usual DBP of 10 mm Hg during middle and advanced age is associated with a twofold increase in the risk of death from stroke, ischemic heart disease, or other vascular causes.\textsuperscript{8}

The JNC 7 and other major treatment guidelines emphasize the importance of achieving the minimal BP goal of <140/90 mm Hg in all patients with uncomplicated hypertension.\textsuperscript{1,4,6} The JNC 7 now defines normal BP as <120/80 mm Hg and includes a new category—“prehypertension”—for those individuals with SBP between 120 and 139 mm Hg and with DBP between 80 and 89 mm Hg.\textsuperscript{1}

Large population-based studies in the US and United Kingdom have indicated that prehypertension is associated with an increased risk of cardiovascular disease,\textsuperscript{9,10} and that there is overlap between this category and mild (stage 1) hypertension with respect to cardiovascular event risk.\textsuperscript{9,10} It has been suggested that early pharmacologic treatment of prehypertension (particularly within the BP range defined in the past as “high normal,” that is, SBP of 130 to 139 mm Hg or DBP of 85 to 89 mm Hg) may help to prevent the development of clinical hypertension and its long-term cardiovascular consequences.\textsuperscript{9,10} At least one study is underway to test this hypothesis: 1000 patients with prehypertension are being treated with the angiotensin II receptor blocker (ARB) candesartan or placebo for 2 years and the incidence of hypertension assessed during a 2-year follow-up period. The study will be completed in 2004.\textsuperscript{11} Currently, JNC 7, the American Diabetes Association, and the National Kidney Foundation recommend a more aggressive BP goal of <130/80 mm Hg for hypertensive patients with diabetes or chronic kidney disease.\textsuperscript{1,12,13} The guidelines of the International Society on Hypertension in Blacks also recommend aggressive treatment of hypertension in African Americans, often requiring initiation of therapy with at least two medications.\textsuperscript{14}

Despite concerns about the economic burden of implementing lower BP goals, treatment to the lower BP goal recommended for high-risk patients in the earlier JNC VI Report (BP <130/85 mm Hg) appears to be cost-effective in the long term, especially in older patients. An economic analysis showed that treating high-risk (diabetic) patients age ≥60 years to a BP goal of <130/85 mm Hg, rather than the previously accepted goal of <140/90 mm Hg, resulted in cost savings over a patient’s lifetime.\textsuperscript{15} The cost-effectiveness ratio was US $1664 per life-year gained, well within the internationally accepted range for cost-effective therapies. However, in the NHANES III survey, only 11% of diabetic patients achieved the then-recommended goal of <130/85 mm Hg.\textsuperscript{16}

Reduction of SBP to target levels is more difficult to achieve than DBP but is associated with greater reduction of cardiovascular risk than DBP in persons age >50 years.\textsuperscript{1,17-23} This is an important consideration in that systolic hypertension is highly prevalent in this age group.\textsuperscript{24} In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), 66% of the 33,357 participants achieved BP control (<140/90 mm Hg) at 5 years. Approximately 33% of patients still had SBP ≥140 mm Hg, whereas less than 8% had DBP ≥90 mm Hg at this point.\textsuperscript{25} Even less favorable control rates were achieved in the Losartan Intervention For Endpoint reduction (LIFE) in Hypertension study, in which, at study end (≥4 years), only 46% to 49% of the 9193 participants had achieved the SBP goal of ≤140 mm Hg, although 89% had achieved the DBP goal of ≤90 mm Hg.\textsuperscript{26}

### Requirements for Effective Antihypertensive Therapy

The reasons for poor BP control are multifactorial. Aspects related to patients include socioeconomic factors, age, adherence, and commitment; those pertaining to physicians include lack of familiarity with national hypertension treatment guidelines, failure to treat aggressively, and acceptance of patient BP levels above the recommended targets.\textsuperscript{27-35} Patient adherence to therapy is a key factor and is affected by the efficacy, cost, tolerability, and complexity of the drug regimen.\textsuperscript{33-35}

Therapy is more likely to be successful when explicit BP goals are set and treatment algorithms provided to achieve these goals.\textsuperscript{1,36} For instance, in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study, in which an explicit BP goal of <140/90 mm Hg was set, BP control rates improved in 13,449 patients (92% of whom were receiving antihypertensive therapy at baseline) from 19% at baseline to 61% at 30 months.\textsuperscript{37} After 30 months of goal-oriented therapy, DBP was controlled in 90% of patients compared with 54% at baseline, and SBP was controlled in 62% compared with 22% at baseline. Similarly, goal-oriented therapy in the African American Study of Kidney Disease and Hypertension (AASK) trial was shown to result in effective BP control, even in a hypertensive population whose BP has always been difficult to control.\textsuperscript{38}

Historically, most studies evaluating the efficacy of antihypertensive agents in reducing BP have concentrated on the BP differential achieved between the study drug and a control group/comparator, emphasizing DBP reductions primarily, without concern for the final absolute BP values. Others report BP normalization or control rates that are defined by DBP goals only. In addition, many studies report the proportion of patients responding to a given therapy, ie, the “responder rate,” which is a less stringent
measurement than goal rate attainment. Responder rates typically include patients attaining an arbitrary, predetermined level of change (usually ≥10 mm Hg reduction from baseline in DBP), as well as those patients achieving a set DBP goal (usually DBP ≤90 mm Hg). Thus, a patient may be counted as a responder and still not have reached goal BP. This interpretation of BP control is clearly flawed, as it ignores SBP entirely. Elevated SBP in persons age >50 years is associated with greater cardiovascular risk than elevated DBP.1,17–23 As noted in the Framingham Heart Study population,24,39

The Place of ARB in the Treatment of Hypertension

Among antihypertensive agents, ARB have a unique mechanism: they block the binding of angiotensin II to the angiotensin II type 1 (AT1) receptor and thereby inhibit its activation. Angiotensin II is the primary effector peptide of the renin–angiotensin–aldosterone system (RAAS). Activation of the AT1 receptor by angiotensin II produces acute vasoconstriction and also results in increased salt retention, fluid volume, aldosterone secretion, and sympathetic activity.40,41 Virtually all of the known cardiovascular effects of angiotensin II are mediated by the AT1 receptor. Excessive RAAS activity contributes to the pathogenesis of hypertension, atherosclerosis, coronary artery disease, heart failure, myocardial infarction, and nephropathy.42–44

It has been reported that ARB slow the progression of renal disease associated with hypertension and type 2 diabetes.45–47 Hence, the current American Diabetes Association guidelines recommend that ARB, as well as angiotensin-converting enzyme (ACE) inhibitors, be strongly considered as first-line agents for hypertensive patients with type 2 diabetes and evidence of renal disease.12

The ARB drugs have excellent tolerability, with an adverse event profile similar to that of placebo.41,48 In recent database reviews of the medical records of more than 56,000 patients followed for 1 to 4.5 years, the rate of patient persistence with antihypertensive therapy was significantly higher with ARB than with any of the other classes of agents, including ACE inhibitors, calcium channel blockers, diuretics, and β-blockers.49–51 Furthermore, in three large-scale clinical trials, fewer participants in the ARB groups discontinued the study drug than in the β-blocker (one study) or the ACE inhibitor groups (two studies).56,52,53

Blood Pressure–Lowering Efficacy and Goal Rates With ARB

A literature search was performed using MEDLINE, EMBASE, and BIOSIS to identify articles reporting BP goal rate attainment with ARB. Despite the large volume of literature about ARB and the emphasis placed on achieving BP goals since the publication of JNC V guidelines in 1993,54 there is little comparative information regarding BP goal attainment with ARB in clinical trials. Furthermore, in those studies that do report goal rate data, only results for the achievement of DBP goals (usually either <90 or <85 mm Hg) or responder rates are typically presented.

The Candesartan Versus Losartan Efficacy Comparison (CANDLe) and the Candesartan Losartan Assessment In Multi-Center Program (CLAIM II) studies compared the antihypertensive efficacy of candesartan and losartan potassium and found that approximately one half of the patients in both treatment groups (mean baseline seated DBP of 100 mm Hg in both studies) achieved a DBP of ≤90 mm Hg after 8 weeks of treatment.55,56 In both studies, treatment was initiated with 16 mg candesartan or 50 mg losartan potassium. The dose was doubled after 2 weeks in all patients in CLAIM II,55 whereas the dose was increased in the CANDLE study only if DBP was >90 mm Hg after 4 weeks of treatment.56 In the CANDLE study, 54% of candesartan and 43% of losartan potassium recipients reached the DBP goal (P = NS);56 corresponding values for CLAIM II were 49% and 44.6% (P = NS).55

In an efficacy study comparing irbesartan and enalapril, a DBP of ≤90 mm Hg was achieved by more than 60% of patients (mean baseline seated DBP 101 mm Hg). During the 12-week trial the initial doses of irbesartan (75 mg) and enalapril (10 mg) could be doubled at week 4 and/or week 8 if DBP remained >90 mm Hg. By the end of treatment, 66% of irbesartan recipients and 63% of enalapril recipients had achieved the DBP goal (P = NS).57 Irbesartan and enalapril were also compared in an 8-week study of elderly (≥65 years) patients with hypertension (mean baseline seated DBP, 99 mm Hg). In this study, patients commenced treatment with irbesartan 150 mg or enalapril 10 mg; this dose could be doubled at week 4 if DBP remained >90 mm Hg. After 8 weeks, 52.9% of irbesartan and 54.9% of enalapril recipients had a seated DBP of ≤90 mm Hg (P = NS).58

A 24-h ambulatory DBP of ≤85 mm Hg was achieved by 71% of patients treated with telmisartan (40 to 120 mg/day) for 12 weeks in a study conducted by Lacourcière et al (note: mean baseline BP was not given; inclusion criteria specified a baseline seated DBP 95 to 114 mm Hg). This result compared favorably with the comparator agent amlodipine besylate (5 to 10 mg/day), which led to 55% of the recipients reaching the DBP goal (P = NS). However, it should be noted that 20.5% of patients already had a mean 24-h ambulatory DBP of <85 mm Hg at baseline.59

An efficacy study comparing the recommended starting doses of olmesartan medoxomil (20 mg/day), amlodipine besylate (5 mg/day) and placebo presented data for the achievement of SBP and DBP goals (mean baseline 24-h ambulatory SBP/DBP ~154/95 mm Hg).60 After 8 weeks of treatment with olmesartan medoxomil, 67.3% of the patients had an ambulatory DBP <90 mm Hg and 50.9%
had an ambulatory SBP <140 mm Hg. Corresponding rates for amlodipine besylate were 64.0% and 50.0% (P = NS for amlodipine besylate vs. olmesartan medoxomil). The more rigorous DBP goal of <85 mm Hg was achieved by significantly more olmesartan medoxomil patients compared with amlodipine besylate patients (48.0% v 34.3%; P = .01). Similarly, the more rigorous SBP goal of <130 mm Hg was achieved by significantly more olmesartan medoxomil patients compared with amlodipine besylate patients (33.9% v 17.4%; P < .001). The higher goal rate attainment reported for the olmesartan medoxomil–treated patients occurred despite the finding that both treatment groups demonstrated a similar mean 24-h ambulatory reduction in BP at 8 weeks (DBP: −7.7 and −7.0 mm Hg and SBP: −12.2, and −12.3 mm Hg, respectively). This finding of higher goal rate attainment was due to the differing distributions of ambulatory BP response seen with the two drugs. More specifically, a greater number of patients in the amlodipine besylate group than in the olmesartan medoxomil group showed only modest decreases (±6 mm Hg) in ambulatory DBP from baseline, whereas more olmesartan medoxomil–than amlodipine besylate–treated patients had decreases of 13 to 18 mm Hg in ambulatory DBP, and twice as many olmesartan medoxomil–treated patients had decreases of ≥19 mm Hg. As a result, even though both treatment groups demonstrated similar mean reductions in BP, the observed difference in the distribution of BP response translated into an increased number of patients achieving BP goals in the olmesartan medoxomil group.

To determine the proportion of patients achieving combined SBP/DBP goals with ARB monotherapy, a secondary analysis was performed on BP efficacy data obtained from a clinical trial previously published by Oparil et al.61 This study compared the antihypertensive effect of olmesartan medoxomil, losartan potassium, valsartan, and irbesartan in a multicenter, randomized, double-blind, head-to-head design in 588 patients with mild to moderate essential hypertension (mean baseline cuff BP 157/104 mm Hg). Patients received the recommended starting doses of olmesartan medoxomil (20 mg/day), losartan potassium (50 mg/day), valsartan (80 mg/day), or irbesartan (150 mg/day) once daily for 8 weeks. At study end, the reduction from baseline in mean sitting cuff DBP (Fig. 1A) at trough (24 to 27 h post-dose) with olmesartan medoxomil (11.5 mm Hg) was significantly greater compared with losartan potassium (8.2 mm Hg; P < .0005), valsartan (7.9 mm Hg; P < .0005), or irbesartan (9.9 mm Hg; P < .05). The reduction in sitting cuff SBP (Fig. 1A) with olmesartan medoxomil (11.3 mm Hg) was numerically greater than with losartan potassium (9.5 mm Hg), valsartan (8.4 mm Hg), or irbesartan (11.0 mm Hg).61

As shown in Fig. 2A, a secondary analysis of the data from the Oparil et al study61 showed that the recommended SBP/DBP goal of <140/90 mm Hg was achieved by 32.4% of olmesartan medoxomil patients compared with 16.1% of losartan potassium patients (P = .002), 14.5% of valsartan patients (P < .001), and 25.9% of irbesartan patients (P = NS) (data on file; Sankyo Pharma Inc.). Thus, twice as many olmesartan medoxomil patients achieved the standard JNC 7 goal of <140/90 mm Hg compared with either losartan potassium or valsartan patients, whereas approximately 25% more olmesartan medoxomil than irbesartan patients achieved this goal. A similar pattern was seen for the more rigorous <130/85 mm Hg goal, with 12.5%, 4.4%, 3.1%, and 9.4% of the patients assigned to olmesartan medoxomil, losartan potassium, valsartan, and irbesartan, respectively, achieving this goal (Fig. 2B). Almost three times as many olmesartan medoxomil–treated patients reached this goal.
assessed using ambulatory BP monitoring. Data for the moderate essential hypertension. (multicenter, placebo-controlled study in 588 patients with mild-to-moderate essential hypertension). Results from a randomized, double-blind, placebo-controlled study in 588 patients with mild-to-moderate essential hypertension. irbesartan 150 mg (mean seated cuff BP measurement; data on file, Sankyo Pharma Inc.). Results from a randomized, double-blind, placebo-controlled study in 588 patients with mild-to-moderate essential hypertension. The adverse event profile of ARB is similar to that of the other major classes of antihypertensive agents (ACE inhibitors, β-blockers, calcium channel blockers, diuretics) but with a better tolerability profile. The adverse event profile of ARB is similar to that of placebo, and the incidence of troublesome cough and angioedema is significantly lower with ARB than with ACE inhibitors. The high efficacy and excellent tolerability of ARB have contributed to both the enhanced patient adherence and low discontinuation rates associated with their use in clinical studies.

A. BP Goal <140/90 mm Hg

![A BP Goal <140/90 mm Hg](image1)

B. BP Goal <130/85 mm Hg

![B BP Goal <130/85 mm Hg](image2)

FIG. 2 Proportion of patients achieving goal blood pressures (BP) of <140/90 mm Hg and <130/85 mm Hg after 8 weeks of once-daily therapy with olmesartan 20 mg, losartan 50 mg, valsartan 80 mg, or irbesartan 150 mg (mean seated cuff BP measurement; data on file, Sankyo Pharma Inc.). Results from a randomized, double-blind, multicenter, placebo-controlled study in 588 patients with mild-to-moderate essential hypertension. (A) Goal rates for BP <140/90 mm Hg. (B) Goal rates for BP <130/85 mm Hg. *P = .002 vs. olmesartan medoxomil; †P < .001 vs. olmesartan medoxomil; ‡P = .001 vs. olmesartan medoxomil; ††P = .002 vs. olmesartan medoxomil; §P = .008 vs. olmesartan medoxomil.

compared with those given losartan potassium (P = .021) or valsartan (P = .008), and almost one third more compared with patients given irbesartan (P = NS).

Reductions in BP after 8 weeks of therapy were also assessed using ambulatory BP monitoring. Data for the 24-h ambulatory BP measurements were similar to those recorded for cuff BP. As shown in Fig. 1B, the reduction in mean 24-h ambulatory DBP was significantly greater for olmesartan medoxomil compared with losartan potassium (P = .0029) or valsartan (P = .0002) and were numerically greater than for irbesartan (P = NS). Likewise, 24-h ambulatory SBP (Fig. 1B) was reduced to a significantly greater extent with olmesartan medoxomil compared with losartan potassium (P = .0028) or valsartan (P = .0003) and was numerically greater than with irbesartan (P = NS). The impressive BP reductions and goal attainment achieved with the 20-mg olmesartan medoxomil starting dose in this study would be expected to be exceeded if the olmesartan medoxomil dose were either up-titrated or a second complementary agent, particularly a thiazide-type diuretic, were added, in keeping with the JNC 7 recommendations.

Discussion

In recent years, much emphasis has been placed on controlling BP to below goal levels to prevent cardiovascular disease. A high level of concern has been expressed over what is considered to be an inadequate level of BP control in patients with hypertension, on both a national and worldwide basis. However, few studies of antihypertensive therapies assess, or at least report, the degree of success in achieving these target BP goals in the treated populations. An important measure of the efficacy of an antihypertensive therapy, at least from a clinical practice perspective, is its ability to achieve BP reduction to below recommended BP goals, both diastolic and systolic, in a high proportion of patients.

Much of the recent research activity in hypertension has centered on the ARB. The members of this new class of drug, like ACE inhibitors, modulate the RAAS; but they differ from ACE inhibitors in that they inhibit the actions of angiotensin II at the AT₁ receptor site rather than inhibiting the production of the mediator. The antihypertensive efficacy of ARB has been shown to be at least equivalent to that of the other major classes of antihypertensive agents (ACE inhibitors, β-blockers, calcium channel blockers, diuretics) but with a better tolerability profile. The adverse event profile of ARB is similar to that of placebo, and the incidence of troublesome cough and angioedema is significantly lower with ARB than with ACE inhibitors. The high efficacy and excellent tolerability of ARB have contributed to both the enhanced patient adherence and low discontinuation rates associated with their use in clinical studies.

Trials such as Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and Irbesartan Diabetic Nephropathy Trial (IDNT) are part of a growing evidence base indicating that ARB provide renal protection beyond that induced by BP reduction alone. IDNT and RENAAL showed that ARB slow the progression of renal disease in patients with diabetic nephropathy; the Irbesartan in patients with type 2 diabetes and MicroAlbuminuria study (IRMA 2) and MicroAlbuminuria Reduction with VALsartan study (MARVAL) showed that these agents also delay the development of nephropathy in diabetic patients with microalbuminuria. These renoprotective effects were independent of BP lowering; and in the MARVAL trial, significantly greater effects on albumin excretion were seen with valsartan than with amlodipine, despite similar reductions in BP.

Long-term clinical outcomes trials have also demonstrated the benefits of ARB in patients with heart failure. The Valsartan in Heart Failure Trial (Val-HeFT) found that valsartan added to pre-existing therapy was more effective than placebo in reducing the combined endpoint...
of mortality and morbidity in patients with heart failure and left ventricular (LV) systolic dysfunction.\(^6\) The Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) studies have demonstrated the effectiveness of candesartan in reducing cardiovascular deaths and hospital admissions for heart failure in patients with varying degrees of heart failure.\(^5\)–\(^7\)

Evidence is also emerging that ARB may have a role in secondary prevention after myocardial infarction. The Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) found a non-significant difference in total mortality in favor of the ACE inhibitor captopril over losartan potassium in patients with evidence of heart failure or LV dysfunction after acute myocardial infarction, although the incidence of revascularization, reinfarction, and all-cause hospital admission were essentially the same in the two groups.\(^8\) The authors commented that the maximal dose of losartan potassium (50 mg once daily) and relatively slow up-titration might have resulted in a suboptimal effect, emphasizing the potential importance of adequate dosage and rapid titration. In The Valsartan in Acute Myocardial Infarction Trial (VALIANT), valsartan titrated to a maximal dose of 160 mg twice daily was as effective as captopril (50 mg three times daily, same dosage as in OPTIMAAL) for the prevention of mortality and cardiovascular events in patients with myocardial infarction complicated by heart failure or LV dysfunction.\(^9\) Thus, at optimal doses, the ARB are establishing a role in the prevention of sequelae in post-myocardial infarction patients with LV dysfunction.

The LIFE study found that losartan potassium was more effective than atenolol for the prevention of cardiovascular morbidity and mortality in patients with hypertension and LV hypertrophy, particularly in reducing the incidence of stroke.\(^2\) Compared with atenolol, there was a nonsignificant trend towards lower overall mortality and cardiovascular mortality favoring losartan, as well as a 25% reduction in the risk of new-onset diabetes (\(P = .001\)). Therefore, ARB have proven clinical advantages in terms of reducing cardiovascular and metabolic endpoints, independent of their impact on BP.

The similar outcomes seen with multiple ARB in randomized controlled trials suggest a class effect for the ARB in cardiovascular and renal protection. Although many of these trials included treatment algorithms designed to achieve target BP in the study patients, BP control—particularly control of SBP—was achieved by only 48% to 66% of patients in the trials for which it was reported, despite the use of up to three antihypertensive agents. In clinical trials, ARB have produced reductions in BP that were similar to those achieved with other antihypertensive agents but have proved to be more effective than a \(\beta\)-blocker in reducing cardiovascular endpoints\(^2\) and more effective than a calcium channel antagonist in delaying renal disease.\(^6\) In contrast, the large-scale Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE) trial demonstrated that calcium channel antagonists are no more effective than a diuretic or a \(\beta\)-blocker in reducing cardiovascular risk.\(^7\)

This review has demonstrated that monotherapy with an ARB is capable of achieving both DBP and SBP goals in a significant proportion of patients. Although outside the scope of this review, the addition of hydrochlorothiazide to ARB monotherapy can result in DBP and SBP goal rate attainment of up to 80% and 87%, respectively.\(^7\) This represents a clinically significant improvement over monotherapy and is in line with JNC 7 guidelines, which emphasize the importance of achieving BP goals via up-titrating initial drug dosages and, when necessary, adding a complementary antihypertensive agent.

There is clearly a need for more head-to-head comparative studies of antihypertensive agents with goal rates (both SBP and DBP) as the primary efficacy variable, for both monotherapy and fixed combinations, as well as more complex, multidrug regimens. An ARB-based regimen may be a good candidate for such a treatment algorithm because of its high efficacy and excellent tolerability. The achievement of BP goals—particularly combined BP goals as specified by JNC 7—needs to become the primary day-to-day objective in hypertension treatment.

References


