Reaching for Aggressive Blood Pressure Goals: Role of Angiotensin Receptor Blockade in Combination Therapy

By Richard V. Milani, MD

Abstract
Elevated blood pressure, particularly systolic blood pressure, increases the risk of cardiovascular and renal complications in patients with diabetes. Current national guidelines set the blood pressure goal for those with diabetes at <130/80 mm Hg, which is lower than the goal for the general population (<140/90 mm Hg). Achieving this goal, however, remains difficult, with blood pressure control rates being lower for patients with diabetes than for those without diabetes. Large clinical trials have demonstrated that in most cases, patients will require 2 or more antihypertensive agents to achieve goal blood pressure. The renin-angiotensin-aldosterone system plays a key role in regulation of blood pressure. The angiotensin AT$_1$ receptor blockers (ARBs), which block the effects of angiotensin II, not only lower blood pressure but also provide target-organ protection. These agents are generally well-tolerated, with a side effect profile similar to placebo. Clinical comparisons of different drugs within the class have shown that olmesartan, the newest ARB, produced greater reductions in blood pressure than other agents and that a greater percentage of patients treated with olmesartan reached target blood pressure. Combining an ARB with a diuretic may allow more patients to reach goal blood pressure.

ease were 2 to 6 times greater in subjects with isolated systolic hypertension than in those with an isolated DBP elevation. Similar findings have been observed in the Multiple Risk Factor Intervention Trial (MRFIT). The risk of cardiovascular mortality for patients with SBP of 140 to 160 mm Hg was 81% greater than that of patients with SBP values ≤140 mm Hg; those with SBP >160 mm Hg had a 94% greater risk of CVD after adjusting for age, associated risk factors, and DBP. When adjusting for SBP levels, CVD and coronary heart disease risk were not associated with changes in DBP. Examination of the database from the Irbesartan Diabetic Nephropathy Trial (IDNT) shows the same large contribution of SBP to renal outcomes.

The relationship between blood pressure and cardiovascular events is continuous, and the cost of not achieving goal blood pressure is high in terms of adverse clinical events. Although blood pressure goals may seem aggressive, the risk of CVD actually starts at a blood pressure of 115/75 mm Hg. Lewington and colleagues found that ischemic heart disease mortality increased linearly at all ages starting at SBP >115 mm Hg and DBP >75 mm Hg. In individuals aged 40 to 69 years, ischemic heart disease mortality doubled with every 20-mm Hg increase in SBP and every 10-mm Hg increase in DBP.

In a 14-year follow-up analysis of 6859 participants in the Framingham Heart Study, Vasan et al demonstrated a continuous gradient of increasing cardiovascular risk across blood pressure categories that were classified in JNC VI as high normal (130-139/85-89 mm Hg), normal (120-129/80-84 mm Hg), and optimal (<120/80 mm Hg). Therefore, getting patients to their goal blood pressure with some urgency should be the objective in treating patients with hypertension.

**Inadequacy of Monotherapy**

Because hypertension is a multifactorial disease, in the vast majority of cases, achieving goal blood pressure will require the use of at least 2 antihypertensive drugs.
(HOT) study, 12 18,790 patients were randomly assigned to 3 different DBP targets (≤90, ≤85, or ≤80 mm Hg) with a felodipine-based regimen of antihypertensive agents. Baseline blood pressure was a mean of 161/98 mm Hg in the 6000 subjects who were receiving treatment at baseline, and approximately 40% were receiving more than 1 antihypertensive drug. At 5 years, combination therapy was required to achieve goal DBP in up to three fourths of participants, depending on the goal to which they were randomized. Only about one fourth of patients randomized to a goal DBP ≤80 mm Hg were receiving monotherapy at the end of the study.

In the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE), 13 68% of the study participants achieved a goal SBP of <140 mm Hg at 3 years. Single-drug therapy was used in only 24% of the study population; 44% were taking 2 drugs, and the remaining 32% were taking 3 or more drugs by the end of the study.

Data from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) 14 show a similar pattern. Twenty-seven percent of ALLHAT participants had a baseline blood pressure <140/90 mm Hg; by 5 years, this proportion increased to 66% with use of a mean of 1.6 drugs per patient. As expected, SBP goal was much more difficult to achieve than DBP goal.

Bakris and colleagues examined the number of antihypertensive drugs needed to reach target across several studies in patients with renal disease or diabetes. 15 In the trials examined, patients usually required 3 or 4 drugs to reach target blood pressure (Figure 3).

**Strategies to Achieve Goal Blood Pressure**

The renin-angiotensin-aldosterone system (RAAS) plays a central role in the physiology and pathophysiology of the cardiovascular system. Most of the effects of the RAAS are mediated by angiotensin II, a potent vasoconstrictor that acts directly on blood vessels to control peripheral vascular resistance. Angiotensin II also has indirect pressor effects that are mediated by activation of the sympathetic nervous system and by controlling the secretion of aldosterone (and hence salt and water homeostasis). Angiotensin II also acts as a growth factor and is involved in remodeling processes in the heart and blood vessels.

Angiotensin AT₁ receptor blockers (ARBs), which block the effects of angiotensin II at the receptor level, are effective antihypertensive agents, as demonstrated in numerous clinical trials. They exhibit dose-dependent efficacy with tolerability comparable with that of placebo, and the rate of persistence with ARBs is greater than that with agents from other antihypertensive classes. 16-18

An analysis of the literature performed by Oparil 19 found that ARB monotherapy generally results in attainment of DBP <90 mm Hg in about 50% of hypertensive patients. At starting doses, reductions in sitting cuff SBP from baseline were 8.4 to 11.3 mm Hg, depending on the ARB, and reductions in sitting cuff DBP were 7.9 to 11.5 mm Hg (Figure 4).

One of the recommendations in JNC 7 is to initiate combination therapy as first-line treatment in patients with stage 2 hypertension, defined as a blood pressure of ≥160/100 mm Hg. Coadministration of 2 agents with differing mechanisms increases the antihypertensive effects of both agents.

Adding a diuretic to an ARB markedly and dose-dependently increases the blood pressure-lowering effect of the ARB. In a meta-analysis of 43 published randomized controlled trials, 20 hydrochlorothiazide added to

**Figure 3. Average Number of Antihypertensive Agents Needed to Achieve BP Goals**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Antihypertensive Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Kingdom Prospective Diabetes Study</td>
<td></td>
</tr>
<tr>
<td>(≤85 mm Hg [diastolic BP])</td>
<td></td>
</tr>
<tr>
<td>Appropriate Blood Pressure Control in Diabetes Trial</td>
<td></td>
</tr>
<tr>
<td>(&lt;75 mm Hg [diastolic BP])</td>
<td></td>
</tr>
<tr>
<td>Modification of Diet in Renal Disease Study</td>
<td></td>
</tr>
<tr>
<td>(&lt;92 mm Hg [mean arterial pressure])</td>
<td></td>
</tr>
<tr>
<td>Hypertension Optimal Treatment Study</td>
<td></td>
</tr>
<tr>
<td>(&lt;80 mm Hg [diastolic BP])</td>
<td></td>
</tr>
<tr>
<td>African American Study of Kidney Disease</td>
<td></td>
</tr>
<tr>
<td>(&lt;92 mm Hg [mean arterial pressure])</td>
<td></td>
</tr>
</tbody>
</table>

BP indicates blood pressure.

Reproduced, with permission, from Bakris GL, et al. 15
various ARBs reduced SBP by 16.1 to 20.6 mm Hg and DBP by 9.9 to 13.6 mm Hg.

In a controlled study of olmesartan/hydrochlorothiazide in hypertensive patients, the 40-mg/12.5-mg dose produced a significant \((P < .001)\) 19/18-mm Hg reduction from baseline blood pressure, and the 40-mg/25-mg dose demonstrated a significant \((P < .001)\) 27/22-mm Hg reduction from baseline.

**ARBS and Target-organ Protection**

Outcomes data demonstrate cardiovascular and end-organ protection with the use of ARBs, providing clinical rationale for their use in the treatment of hypertension.

The Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study (IRMA 2) is a defining study that demonstrated the impact of an ARB (irbesartan) on proteinuria with appropriate dosing. IRMA 2 examined patients with hypertension, type 2 diabetes, and microalbuminuria, defined as an albumin excretion rate of 20 to 200 \(\mu\)g/min, and normal renal function. Patients were randomly assigned to a control group or treatment with irbesartan 150 or 300 mg/day.

The risk of achieving the primary end point—progression to clinical proteinuria—was reduced by 70% in the group randomized to 300 mg/day of irbesartan compared with placebo. Achievement of normoalbuminuria was possible in 34% of patients who received the 300-mg/day dosage of irbesartan (Figure 5). The beneficial effects on renal function appeared to be independent of the effect on blood pressure, because blood pressure reduction was similar in all 3 groups.

A substudy of IRMA 2 analyzed albumin excretion rates 1 month after stopping all treatments. The group that received conventional antihypertensive treatment and those that received conventional antihypertensive therapy plus 150 mg/day of irbesartan had urinary albumin excretion rates return to baseline 1 month after cessation of therapy. The patients assigned to irbesartan 300 mg/day maintained a 50% reduction in albumin excretion rate at 1 month, suggesting preservation of kidney tissue at the higher dose.

Another study, IDNT was conducted to determine whether the use of an ARB would protect against the progression of nephropathy in patients with hypertension and type

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**Figure 4.** Comparison of Starting Dose ARBs: Mean Change in Cuff DBP and SBP at Week 8

<table>
<thead>
<tr>
<th>ARB</th>
<th>20 mg/day (n = 145)</th>
<th>50 mg/day (n = 146)</th>
<th>80 mg/day (n = 142)</th>
<th>150 mg/day (n = 145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLM</td>
<td>-11.3 (P &lt; .118)</td>
<td>-9.5 (P &lt; .032)</td>
<td>-8.4 (P &lt; .425)</td>
<td></td>
</tr>
<tr>
<td>LOS</td>
<td>-11.5 (P &lt; .001)</td>
<td>-9.9 (P &lt; .041)</td>
<td>-8.2 (P &lt; .001)</td>
<td></td>
</tr>
<tr>
<td>VAL</td>
<td>-11.0 (P &lt; .425)</td>
<td>-7.9 (P &lt; .118)</td>
<td>-7.9 (P &lt; .001)</td>
<td></td>
</tr>
<tr>
<td>IRB</td>
<td>-11.0 (P &lt; .425)</td>
<td>-7.9 (P &lt; .118)</td>
<td>-7.9 (P &lt; .001)</td>
<td></td>
</tr>
</tbody>
</table>

*Significant vs olmesartan medoxomil.
†Nonsignificant vs olmesartan medoxomil.
Mean baseline BP equals 156-157/104 mm Hg.
ARBS indicates angiotensin II receptor blockers; DBP, diastolic blood pressure; BP, blood pressure; SBP, systolic blood pressure; SeDBP, seated diastolic blood pressure; SeSBP, seated systolic blood pressure; OLM, olmesartan medoxomil; LOS, losartan potassium; VAL, valsartan; IRB, irbesartan.
In this study, patients were randomly assigned to receive irbesartan, amlodipine, or placebo with a target blood pressure of <135/85 mm Hg.

The risk of reaching the primary end point (a composite of a doubling of serum creatinine level, development of end-stage renal disease, or death) was significantly lower in the irbesartan group compared with the amlodipine group ($P = .006$) and placebo group ($P = .02$), mainly because of a reduction of the progression of renal dysfunction. No difference in the risk of mortality was observed between the groups. This study therefore established the efficacy of irbesartan to prevent the progression of nephropathy in patients with type 2 diabetes.

In IDNT, a 48% reduction in the risk of progressing to a renal end point was observed for every 20-mm Hg reduction in SBP, whereas DBP had little impact. The same strong association between SBP and progression of renal disease was confirmed in patients without diabetes. Further analysis revealed that the risk of renal outcomes was influenced more by follow-up SBP than by baseline SBP. Patients who had an achieved mean SBP in the lowest quartile (<132 mm Hg) had one third the risk of a doubling of serum creatinine or progressing to end-stage renal disease compared with patients in the highest quartile of mean achieved SBP (>149 mm Hg). The relationship between the mean follow-up SBP and the risk of a renal end point was linear all the way down to the lowest SBP levels achieved (<121 mm Hg).

The Reduction of End Points in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study randomized patients with type 2 diabetes and nephropathy to either a losartan-based regimen (50-100 mg once daily) or placebo in addition to conventional antihypertensive therapy. At 3.4 years of follow-up, losartan was associated with a 16% reduction ($P = .02$) in the primary composite end point of time to doubling of serum creatinine concentration, end-stage renal disease, or death. The benefit exceeded that attributable to reduction in blood pressure.

Losartan was also studied in high-risk hypertensive patients in the Losartan Intervention For Endpoint reduction in Hypertension (LIFE) study, which included patients aged 55 to 80 years with essential hypertension and left ventricular hypertrophy. Patients were randomly assigned to regimens beginning with losartan, titrated to 100 mg/day, or atenolol 50 mg/day.

Blood pressure reductions were similar in the 2 groups. Losartan was superior at reducing the incidence of the composite primary end point (cardiovascular mortality, stroke, or myocardial infarction) compared with atenolol, the difference being driven by a significant reduction in stroke (relative risk: 0.87; $P = .021$) with losartan.

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) was a study of 15,245 high-risk patients with hypertension, 92% of whom were receiving antihypertensive therapy before entering the study. They were randomized to a regimen starting with either valsartan 80 mg/day or amlodipine 5 mg/day with elective titration to a target blood pressure of <140/90 mm Hg. Despite a clear blood pressure-lowering advantage with amlodipine, the incidence of cardiac morbidity and mortality was not significantly different between the 2 treatment groups. Fewer valsartan-treated patients were hospitalized for heart failure. A key finding in VALUE was that a rapid reduction in blood pressure was associated with more favorable cardiovascular and mortality out-
comes throughout the course of the entire study.

In both LIFE and VALUE, the ARB-based regimens were associated with significant reductions in new-onset diabetes versus their comparators.

Relative Blood Pressure-Lowering Effects Within the ARB Class

The antihypertensive efficacy of different members of the ARB class has been compared in clinical trials.

In a multicenter, randomized trial, Elliott and colleagues found that starting titrated doses of valsartan and losartan were similarly effective in reducing seated SBP and DBP.28 Candesartan was more effective than losartan in reducing trough seated DBP at 8 weeks (−11.0 mm Hg with candesartan vs −8.9 mm Hg with losartan) in a multicenter, randomized study with treatment titrated to effect.29 Responder rates, defined as the percentage of patients with seated DBP <90 mm Hg, were 64% and 54% with candesartan and losartan, respectively.

Irbesartan and the angiotensin-converting enzyme inhibitor enalapril each resulted in more than 60% of patients achieving a DBP ≤90 mm Hg in a 12-week head-to-head comparison.30 In an 8-week study comparing these 2 agents in elderly (≥65 years) patients with hypertension, 52.9% of irbesartan-treated patients and 54.9% of enalapril-treated patients achieved a seated DBP ≤90 mm Hg.

A secondary analysis of a trial that directly compared starting doses of 4 ARBs used as monotherapy demonstrated that a combined SBP/DBP goal of <140/90 mm Hg could be attained in 32.4% of patients treated with olmesartan medoxomil, 25.9% treated with irbesartan, 16.1% treated with losartan potassium, and 14.5% treated with valsartan.29 A similar pattern was observed for the more rigorous goal of <130/85 mm Hg.29 Considering the total follow-up of 4695 randomized patients, immediate compared with delayed antihypertensive treatment reduced the occurrence of stroke and cardiovascular complications by 28%. In VALUE, also, patients who reached goal within a relatively short time also experienced fewer cardiovascular events than those who achieved goal later.27

In a comparison of olmesartan 20 mg/day, valsartan 80 mg/day, losartan 50 mg/day, and irbesartan 150 mg/day, more patients reached the cuff blood pressure goal of <140/90 mm Hg at week 2 in the olmesartan group (29%) compared with the losartan (13.9%), valsartan (19% P = not significant [NS]), and irbesartan (18.6%) groups (Figure 6).35 Furthermore, more patients reached the more stringent cuff
blood pressure goal of <130/85 mm Hg in the olmesartan group (9.7%) compared with the losartan potassium (2.1%), valsartan (3.5%), and irbesartan (6.2%; \( P = \text{NS} \)) groups. At week 2, olmesartan was significantly more effective than each of the other 3 ARBs in reducing seated SBP and DBP.

**Conclusion**

The risk of cardiovascular events increases linearly with blood pressure. Achieving target blood pressure goals is associated with improved clinical outcomes. In most cases, multiple antihypertensive agents will be required to achieve goal blood pressures, especially in patients with diabetes.

The ARBs have demonstrated blood pressure-lowering efficacy and offer target-organ protection. In clinical trials, ARBs have reduced the incidence of adverse renal and cardiovascular outcomes versus comparators, independent of their effect on blood pressure. These agents are generally well-tolerated, with a side effect profile comparable with placebo. The addition of hydrochlorothiazide improves the blood pressure-lowering efficacy of ARBs and allows more patients to achieve goal blood pressures. Comparative studies of ARBs show differences in the percentage of patients who achieve goal blood pressures, with olmesartan, the newest ARB, being the most potent.

A study of patients >60 years of age with diabetes showed that treatment to a blood pressure goal of <130/85 mm Hg rather than a less stringent goal of <140/90 mm Hg resulted in cost savings over a patient's lifetime. Treatment to the lower goal of <130/80 mm Hg recommended by JNC 7 may prove to be even more cost effective in improving long-term outcomes.

**REFERENCES**


