Angiotensin Receptor Blockers - Advantages of the New Sartans

Zia Al Sabbah*, Aijaz Mansoor**, Upendra Kaul**

Abstract
Advantages of the new angiotensin receptor blockers (ARBs) include once daily dosing, an absence of significant adverse reactions, well tolerated side effect profile and cost effectiveness. A growing realization is their beneficial pleotropic effects. Antihypertensive agents are widely used to reduce the risk of cardiovascular events partly beyond that of blood pressure-lowering. The RAAS, and its primary mediator Ang II, also have a direct influence on the progression of the atherosclerotic process via effects on endothelial function, inflammation, fibrinolytic balance, and plaque stability. For patients at high cardiovascular risk based on the results of the ONTARGET and TRANSCEND studies, telmisartan is indicated for cardiovascular prevention. Studies have shown that olmesartan medoxomil treatment may slow the progression of atherosclerosis and postpone albuminuria thereby potentially improving CV outcomes.

The renin–angiotensin system (RAS) participates significantly in the pathophysiology of hypertension, congestive heart failure, myocardial infarction, and diabetic nephropathy. Angiotensin (Ang) II, induces not only acute vasoconstriction by binding mainly to the ang II type 1 receptor (AT1) but also promotes vascular growth and proliferation, acts as a proinflammatory mediator and causes endothelial dysfunction, leading to cardiovascular disease. Research focused on blocking the RAS led to the discovery of angiotensin-converting-enzyme (ACE) inhibitors, which are effective in the treatment of hypertension and heart failure but are associated with a high frequency of cough and other adverse effects. AT-II-receptor blockers (ARBs) were developed as agents that would more completely block the RAS and decrease the adverse effects seen with ACE inhibitors.

Although both classes of drugs (ACE inhibitors and ARBs) block the RAS, they differ in several important aspects:

- ACE inhibitors reduce the biosynthesis of Ang II by the action of ACE, but do not inhibit alternative non-ACE Ang II-generating pathways. ARBs block the actions of Ang II via the AT1 receptor regardless of the biochemical pathway leading to Ang II formation.
- Unlike ACE inhibitors, ARBs allow activation of AT2 receptors. ARBs cause a several-fold increase in circulating levels of Ang II. Because ARBs block AT1 receptors, this increased level of Ang II is available to activate AT2 receptors. AT2 receptor activation is thought to have the opposite effect of those mediated by the AT1 receptor, which are beneficial to the cardiovascular system and help protect target organs from damage.
- ACE inhibitors increase the levels of a number of ACE substrates, including bradykinin.
- ACE inhibitors may increase Ang (1–7) levels more than do ARBs. ACE is involved in the clearance of Ang (1–7), so inhibition of ACE may increase Ang (1–7) levels more so than do ARBs.

ACE is a relatively nonspecific enzyme that has substrates in addition to angio I, including bradykinin and other tachykinins and thus inhibition of ACE may result in accumulation of these substrates. Production of angiotensin II can occur through non-ACE pathways as well as through primary ACE pathway, and these alternative pathways are unaffected by ACE inhibition. Conversion of AT-I to AT-II is not the only pathway for AT-II generation. AT-II is also formed via pathways involving cathepsin G, elastase, tissue plasminogen activator, chymostatin-sensitive AT-II-generating enzyme, and chymase. Thus, ACE inhibition only partially reduces the formation of AT-II. Agents that can specifically and selectively inhibit the action of AT-II could completely block the RAS. Currently, two classes of drugs have the mechanistic potential to completely block the RAS: renin inhibitors and AT-II-receptor antagonists. ARBs displace angiotensin II from the angiotensin I receptor and produce their blood pressure lowering effects by antagonizing angiotensin II actions (vasoconstriction, aldosterone release, catecholamine release, arginine vasopressin release, water intake and hypertrophic response). ARBs down regulate sympathetic adrenergic activity by blocking the effects of AT-II on sympathetic nerve release and re-uptake of norepinephrine. Although the ARBs have some structural and pharmacokinetic differences, few pharmacological differences separate these agents from one another. Two subtypes of AT-II receptors have been identified. Type 1 receptors are predominantly found on vascular endothelium and are linked to all the known physiological and pharmacologic actions of AT-II. Stimulation of type 1 receptors by AT-II induces vasoconstriction, renal tubular sodium reabsorption, aldosterone release, vascular smooth muscle remodeling, and stimulation of central and peripheral sympathetic activity, thus leading to increases in blood volume and blood pressure. Antagonism of type 1 receptors lowers blood pressure by inhibiting these actions. Type II receptors are predominantly found in the adrenal medulla, uterus, and fetal tissue and may play a role in fetal growth and differentiation, although the exact function of these receptors has not been identified.
There are eight ARBs currently on the market for hypertension and in different cardiovascular indications, ie, losartan, valsartan, candesartan, eprosartan, irbesartan, telmisartan, olmesartan, and azilsartan. All ARBs are approved for the treatment of hypertension. In addition, irbesartan and losartan are approved for diabetic nephropathy, losartan is approved for stroke prophylaxis, and valsartan and candesartan are approved for heart failure and to reduce cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction. ARBs also demonstrated effectiveness in preventing atheromas, decreasing endothelial dysfunction, increasing fibrinolysis, reducing proteinuria, and preserving kidney function in diabetic patients.\(^7\)

Pharmacokinetics of various ARBs are depicted in Table 1. A succinct discussion of the newer ARBs follows.

### Telmisartan

Telmisartan is licensed for the treatment of essential hypertension. Telmisartan, a nonpeptide AT-II-receptor antagonist, gained FDA approval for use in the treatment of hypertension in 1998. Peak plasma levels are obtained 0.5-1 hour after oral administration, and the plasma \( t_{1/2} \) is ~24 hours. Oral bioavailability of ARBs generally is low (<50%, except for irbesartan, with 70% available), and protein binding is high (>90%). Telmisartan is cleared from the circulation mainly by biliary secretion of intact drug. The plasma clearance of telmisartan is affected by hepatic but not renal insufficiency.\(^8\) The recommended oral dosage of telmisartan is 40-80 mg once daily. When further blood pressure reduction is needed (beyond that achieved with 80 mg/day), the addition of hydrochlorothiazide has been found to produce incremental reductions.\(^9\) Telmisartan lowers systolic/diastolic blood pressure in patients with hypertension by up to 12/9 mm Hg at 40 mg once daily, and up to 13/10 mm Hg at 80 mg once daily. It is at least as effective

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**Table 1: Pharmacokinetic properties of the angiotensin II receptor blockers**

<table>
<thead>
<tr>
<th></th>
<th>Losartan</th>
<th>Valsartan</th>
<th>Irbesartan</th>
<th>Candesartan</th>
<th>Eprosartan</th>
<th>Telmisartan</th>
<th>Olmesartan Medosomil</th>
</tr>
</thead>
<tbody>
<tr>
<td>F (%) (bioavailability)</td>
<td>33</td>
<td>10-35</td>
<td>60-80</td>
<td>15</td>
<td>13</td>
<td>42-58</td>
<td>26</td>
</tr>
<tr>
<td>Active metabolite</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>I (metabolite, 3-4)</td>
<td>2-4</td>
<td>1.5-2</td>
<td>3-4</td>
<td>1-2</td>
<td>No</td>
<td>Only 11% biotransformed</td>
</tr>
<tr>
<td>t ½ (hr)</td>
<td>I (metabolite, 6-9)</td>
<td>6</td>
<td>11-15</td>
<td>3.5-4 (metabolite, 3-11)</td>
<td>5-9</td>
<td>No</td>
<td>12-18 (metabolite, 8-13)</td>
</tr>
<tr>
<td>Metabolism (primary pathway)</td>
<td>CYP-2C9 and 3A4</td>
<td>Unknown</td>
<td>CYP 2C9</td>
<td>O-demethylation</td>
<td>Glucoronide conjugation</td>
<td>Conjugation</td>
<td>De-eserifictation</td>
</tr>
<tr>
<td>Elimination (%)</td>
<td>35 renal, 60 biliary</td>
<td>10 renal, &gt;80 biliary</td>
<td>20 renal, 80 biliary</td>
<td>33 renal, 67 biliary</td>
<td>7 renal, 90 biliary</td>
<td>&gt;97 biliary</td>
<td>8-12 renal, biliary</td>
</tr>
<tr>
<td>Food interactions</td>
<td>10% decrease in bioavailability</td>
<td>~50% decrease in AUC (NS)</td>
<td>No</td>
<td>No</td>
<td>Delayed absorption (NS)</td>
<td>6%-20% decrease in Bioavailability</td>
<td>No</td>
</tr>
<tr>
<td>Drug Interactions (significant)</td>
<td>Rifampin, Fluconazole</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Digoxin</td>
</tr>
<tr>
<td>Dose in hepatic impairment</td>
<td>Initial dosage</td>
<td>No change in dose'</td>
<td>No change in dose'</td>
<td>No change in does'</td>
<td>No change in does'</td>
<td>Use with caution</td>
<td>No change in does</td>
</tr>
<tr>
<td>Dose in renal impairment</td>
<td>No change in does</td>
<td>No change in does</td>
<td>No change in does</td>
<td>No change in does</td>
<td>No change in does</td>
<td>No change in does</td>
<td>No change in does</td>
</tr>
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</table>

*No change in dosage for mild to moderate hepatic dysfunction; exercise care in severe disease (no data available); No dosage adjustment necessary unless the patient is volume-depleted. No change in dosage for mild to moderate renal dysfunction; exercise care in severe disease (no data available). AUC= area under the curve; CYP = cytochrome P-450; F= bioavailability; \( t_{1/2} \) = elimination half-life; \( T_{max} \) = time of maximum plasma concentration.
as enalapril, lisinopril, and losartan in the treatment of mild to moderate hypertension. Important clinical studies of telmisartan are shown in Table 2.

**Drug interactions**: No interactions with drugs that inhibit or are metabolized by CYP isoenzymes would be expected, given that CYP isoenzymes are not involved in telmisartan’s metabolism, with the possible exception of interference with the metabolism of drugs metabolized by CYP2C19. When telmisartan is administered with digoxin, peak and trough plasma concentrations of digoxin are increased 49% and 20%, respectively. When telmisartan is given with warfarin there is no evidence of any change in the International Normalized Ratio.

**Adverse effects**: The overall frequency of adverse events with telmisartan 20-160 mg/day was reported to be similar to that with placebo. Rates of upper-respiratory tract infection (7%), dizziness (5%), back pain (3%), sinusitis (3%), and diarrhea (3%) were similar to the rates for placebo (6%, 6%, 1%, 3%, and 2%, respectively). The rate of cough with telmisartan (15.6%) was comparable to that with placebo (9.6%) and significantly less than with lisinopril (60%).

### Table 2: Important clinical trials of Telmisartan

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Patient population</th>
<th>Design</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>DETAIL&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Patients aged 35–80 years, with T2DM, mild to moderate hypertension and early nephropathy; n = 250</td>
<td>Telmisartan or enalapril on a background of antihypertensive treatment; mean/median follow-up not available</td>
<td>Equivalent reduction in the primary endpoint of the change in the GFR from baseline during 5 years of treatment with telmisartan vs enalapril</td>
</tr>
<tr>
<td>AMADEO&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Patients aged 21–80 years, with T2DM, hypertension, or on antihypertensive drugs and overt nephropathy; n 860</td>
<td>Telmisartan or losartan on a background of antihypertensive treatment mean follow-up 0.89 years</td>
<td>Significant reduction in the primary endpoint of the difference in the urinary albumin to creatinine ratio from baseline to week 52 with telmisartan vs losartan despite similar BP reductions in the 2 groups</td>
</tr>
<tr>
<td>VIVALDI&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Patients aged 30–80 years, with T2DM, hypertension and overt nephropathy; n = 885</td>
<td>Telmisartan or valsartan on a background of antihypertensive treatment mean/ median follow-up not available</td>
<td>Equivalent reductions in the primary endpoint of the change from baseline in the 24-hour proteinuria after 12 months for telmisartan and valsartan. Greater renoprotection was seen in those patients with better BP control</td>
</tr>
<tr>
<td>ONTARGET&lt;sup&gt;49&lt;/sup&gt;</td>
<td>High-risk patients aged ≥55 years, with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage; n 25,620</td>
<td>Telmisartan-, ramipril- or telmisartan plus ramipril-based antihypertensive regimens; median follow-up 4.7 years</td>
<td>Telmisartan was equivalent to ramipril for the primary composite endpoint of CV death, MI, stroke, or hospitalization due to HF; it was associated with less angioedema and better treatment adherence. The combination was associated with more adverse events without an increase in efficacy</td>
</tr>
<tr>
<td>TRANSCEND&lt;sup&gt;50&lt;/sup&gt;</td>
<td>High-risk patients aged ≥55 years, with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage, and intolerant to ACE inhibitors; n 5926</td>
<td>Telmisartan regimen or placebo based regimen (on a background of other antihypertensive agents); median follow-up 4.7 years</td>
<td>Equivalent reduction in the primary composite endpoint of CV death, MI, stroke, or hospitalization for HF with telmisartan vs placebo. Significant reduction in the secondary composite endpoint of CV death, MI, or stroke with telmisartan (13%; HR 0.87) vs placebo (14.8%)</td>
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**Olmesartan Medoximil**

In April 2002 the FDA approved Olmesartan medoxomil for the treatment of hypertension. Olmesartan medoxomil, which is administered as a prodrug, is rapidly and completely deresterified to the active metabolite olmesartan during absorption from the gastrointestinal tract. Following the conversion of olmesartan medoxomil to olmesartan, virtually no further metabolism occurs. The bioavailability of olmesartan is approximately 26%, similar to that of losartan and valsartan. Following oral administration, the peak plasma concentration (Cmax) of olmesartan is reached after one to two hours. The bioavailability of olmesartan is not affected by food.<sup>10,11</sup> The plasma t<sub>1/2</sub> is between 10 and 15 hours. Plasma clearance of olmesartan is due to both renal elimination and biliary excretion. Although renal impairment and hepatic disease decrease the plasma clearance of olmesartan, no dose adjustment is required in patients with mild-to-moderate renal or hepatic impairment. The oral dosage of olmesartan medoxomil is 20-40 mg once daily. If BP is not controlled by olmesartan medoxomil alone, a diuretic may be added.

**Adverse Effects**: Based on data from a number of studies, patients have tolerated the drug well, and the incidence of adverse events was similar to that for placebo (42.2% and 42.7%, respectively).<sup>12-15</sup> The most commonly reported side effects were headache, upper respiratory tract infections, and influenza-like symptoms. Dizziness was also frequently noted. Oparil et al<sup>16</sup> found that the rate of dizziness associated with olmesartan medoxomil (1.4%) was similar to the rates for losartan (0.7%), valsartan (1.4%), and irbesartan (3.4%). In clinical trials, the incidence of cough was similar for olmesartan medoxomil (1.4%) was similar to the rates for losartan (0.7%), valsartan (1.4%), and irbesartan (3.4%). In clinical trials, the incidence of cough was similar for olmesartan medoxomil (0.9%) and placebo (0.7%). This rate is much lower than that reported in users of the ACE inhibitors; in those patients, cough has been noted to occur in up to 39% of cases.<sup>18</sup> Angioedema has rarely occurred with ARB therapy, although facial edema has been reported in five patients receiving olmesartan medoxomil.<sup>17</sup>

**Drug Interactions**: Olmesartan medoxomil does not appear to have any clinically relevant drug interactions. The co-administration of antacids does not significantly alter its bioavailability<sup>19</sup> and no clinically significant drug interactions have been reported with the co-administration of digoxin or
warfarin. Because olmesartan medoxomil is not metabolized by the cytochrome P-450 system, drugs that induce, inhibit, or are metabolized by this enzyme do not appear to interact with it.

Clinical Efficacy: Seven placebo-controlled studies involved 2,693 patients with essential hypertension; 2,145 patients received olmesartan medoxomil, and 548 patients received placebo. Doses ranged from 2.5 to 80 mg once daily for six to 12 weeks. Patient responses to olmesartan medoxomil were dose-related; doses of 20 mg daily produced an overall reduction of sitting trough BP (the lowest measured BP with the patient sitting) of about −10/6 mm Hg over placebo, and doses of 40 mg daily produced an overall sitting trough BP reduction of about −12/7 mm Hg over placebo. Doses greater than 40 mg did not offer any additional effects. Various published and unpublished comparative studies have also reported on the antihypertensive efficacy of olmesartan medoxomil.

Clinical trials of Olmesartan

Results from clinical trials suggest that olmesartan medoxomil can be as effective as atenolol (Van Mieghem et al., Püchler et al. and more effective than captopril (Williams et al.), losartan (Ball et al.), valsartan and irbesartan (Oparil et al.) in reducing systolic or diastolic BP. Olmesartan for the Delay or Prevention of Microalbuminuria in Type 2 Diabetes. (ROADMAP) is the first large outcomes trial with olmesartan it was conducted in 4447 patients with type 2 diabetes and one or more additional cardiovascular risk factors, but no evidence of microalbuminuria. Participants could have normal blood pressure or well-controlled hypertension. The primary end point was a renal one, time to onset of albuminuria. Patients were randomized to either 40 mg of olmesartan (n=2232) or placebo (n=2215) daily and were allowed to take additional non-renin-angiotensin system (RAS) antihypertensive medications to reach target BP (<130/80 mm Hg), until the predefined number of adjudicated microalbuminuria events occurred at a median follow-up of 3.2 years. The average baseline BP of participants was 137/80 mm Hg. The results show there was a cumulative incidence of microalbuminuria of 8.2% with olmesartan and 9.8% with placebo; the primary end point, time to onset of microalbuminuria, was delayed by 23% with olmesartan (hazard ratio 0.77, p=0.01), with the majority of this effect being BP. The higher rate of fatal cardiovascular events with olmesartan among patients with preexisting coronary heart disease was noted (15 patients (0.7%) in the olmesartan group as compared with 3 patients (0.1%) (P=0.01) in the placebo group. This excess mortality in the olmesartan group prompted an FDA safety review which is ongoing, and so far, FDA has determined that the benefits of olmesartan continue to outweigh its potential risks when used for the treatment of patients with high blood pressure according to the drug label.

Azilsartan

It is the latest ARB to be approved for hypertension. The key points of Azilsartan are its potency, its ability of sustained blood pressure control over a 24-hour period, and experimental evidence of favorable pleotropic cardioprotective effects. Azilsartan medoxomil at a dose of 40 mg or 80 mg once daily showed greater efficacy (about 10% in absolute rate) than a 320 mg dose of valsartan, the highest approved dose for this drug. Azilsartan is a prodrug that is quickly hydrolyzed to the active moiety azilsartan, a potent and highly selective ARB with estimated bioavailability of 60% and elimination half-life of 12 hours. At the approved dosage, it reduces systolic blood pressure by 12 to 15 mm Hg and diastolic blood pressure by 7 to 8 mm Hg. A higher dose of azilsartan (80 mg) was superior to valsartan 320 mg or olmesartan 40 mg in lowering systolic blood pressure in short-term studies. Additional blood pressure reduction is expected when Azilsartan is used adjunctively with a diuretic. Findings from recent studies suggest that azilsartan medoxomil can lower 24-hour blood pressure more effectively than maximally recommended doses of other ARBs. Experimental studies in animals have revealed the pleotropic effects of Azilsartan. Like improvement in insulin sensitivity and activation of PPAR gamma resulting in a favourable metabolic profile. Azilsartan is well tolerated; the most common side effects are headache and diarrhea. No cases of hyperkalemia have been reported in 6-week clinical trials. Worsening of renal function and hypotension should be monitored, particularly in those with baseline risk factors. There is a lack of human data supporting the use of Azilsartan for improvement in cardiovascular outcomes; therefore, Azilsartan is not approved for indications other than the treatment of hypertension.

Advantages of the Newer ‘Sartans’

Advantages of these drugs include once daily dosing, an absence of significant adverse reactions, well tolerated side effect profile and cost effectiveness. A growing realization is their beneficial pleotropic effects. ARBs are better tolerated than ACE inhibitors and other antihypertensive agents in both the short term and the long term. This is an important benefit, because hypertension is often asymptomatic, making long-term treatment adherence a challenge. None of the ARBs interact with food, which makes oral administration very easy.

The newer agents, Telmisartan, and Olmesartan have longer half-lives and durations of action than the older agents losartan and Valsartan. Twenty-four-hour blood pressure control could be more readily achievable with the newer agents. ARBs are often used in patients who are intolerant of ACE inhibitors due to the development of cough or angioedema, or in those who are at a high risk of developing either of these side effects. Patients over 60 years, females, those of east-Asian ethnicity and smokers are at increased risk of cough, and patients of African-American ethnicity, smokers, or those patients with a history of ACE inhibitor cough are at increased risk of angioedema. Studies in hypertensive patients have shown consistently that Telmisartan improves insulin sensitivity and lipid profiles. Telmisartan has been demonstrated to improve markers of glycemic control, such as glycosylated hemoglobin, in patients with type 2 diabetes. Telmisartan is the only ARB shown to be able to activate PPAR (peroxisome proliferator-activated receptor gamma) at therapeutic dosages, and in general, Telmisartan produces greater beneficial effects on glucose metabolism than the other ARBs.

Clinical evidence for improvements in endothelial function with Telmisartan is provided by the Telmisartan versus Ramipril in renal ENDothelial DYSfunction (TRENDY) study. In the TRENDY® study, Telmisartan not only improved renal endothelial function in patients with type 2 diabetes but also preserved renal function. In comparison with Ramipril, Telmisartan significantly improved resting renal plasma flow, renal vascular resistance, and lowered albuminuria. The Diabetics Exposed to Telmisartan And enalapril (DETAIL) study showed the long-term benefit of Telmisartan in patients with type 2 diabetes and either micro- or macroalbuminuria. GR rate of decline was markedly reduced.

On the basis of the ONTARGET results, Telmisartan...
is proven to have cardiovascular protective effects. The ONTARGET study in patients at high risk of cardiovascular events showed that Telmisartan was non-inferior, as defined by pre-specified boundaries, to the ACEi ramipril given at the same dose as had been proven to be beneficial in the HOPE study. It is as effective as ramipril but is associated with less angioedema and cough. In the TRANSCEND study, Telmisartan was well tolerated among patients who were unable to tolerate ACE inhibitors and their was a significant reduction in the risk of the composite outcomes of cardiovascular death, myocardial infarction, or stroke by 13%.

There is substantial evidence supporting the hypothesis that Ang II plays a significant role in the initiation and progression of atherogenesis, with endothelial dysfunction a hallmark of early event in atherogenesis. Data from the Olmesartan medoxomil clinical trials OLIVUS, EUTOPIA, VIOS, and MORE have demonstrated the specific utility of RAAS suppression in reducing atherosclerotic plaque volume, improving plaque composition and stability, and in improving endothelial dysfunction. These studies have shown that Olmesartan medoxomil treatment may slow the progression of atherosclerosis, thereby potentially improving CV outcomes.

The currently available ARBs have demonstrated their differential efficacy along the cardiovascular and renal disease continua. For patients at high cardiovascular risk based on the results of the ONTARGET and TRANSCEND studies, Telmisartan is indicated for cardiovascular prevention beyond that of blood pressure-lowering alone.

**Combination Therapy**

Combination therapy is an effective strategy to increase antihypertensive efficacy in those patients with poor blood pressure (BP) control. A calcium channel blocker (CCB)/angiotensin receptor blocker (ARB) combination is a rational approach for such an antihypertensive strategy. The ARBs confer stroke protection, renal protection, and tolerability similar to placebo, without dose-related symptomatic and metabolic AEs, while CCBs are beneficial in reducing stroke and treating angina and cardiac ischemia. The antihypertensive efficacy of combinations of once-daily oral amldipine and valsartan (administered as separate agents or as amldipine/valsartan) has been demonstrated in several large, randomized, double-blind clinical trials of 8-16 weeks’ duration; BP reductions were maintained for approximately 1 year in open-label extensions of some of these studies. Combination therapy was more effective than amldipine or valsartan monotherapy in reducing BP in patients with mild to moderate hypertension, and more effective than amldipine monotherapy in reducing BP in patients with moderate to severe (stage 2) hypertension.

**ARBs and CKD**

Activation of the RAAS plays an important role in the progression of CKD regardless of the initial nephropathy, and its blockade remains the most important goal in achieving preservation of renal function.

In 2007, the AHA developed a scientific statement on treating hypertension and designated the CKD population as a high coronary artery disease (CAD) risk group and recommended a blood pressure goal of less than 130/80 mm Hg. Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are preferred antihypertensive agents in patients with CKD as per the NKF KDOQI and JNC 7 guidelines. HIJ-

**Central Aortic Pressure**

The level of augmentation of central systolic blood pressure (SBP) or the central augmentation index (cAI) is caused by reflection of pulse waves in the periphery. Increased pulse wave velocity from stiff large arteries and increased peripheral vascular resistance are two major causes for an earlier return, and higher amplitude of the reflected pulse wave, respectively. Earlier return of the reflected pulse wave shifts central BP augmentation from diastole into late systole, and therefore leads to augmentation of central SBP and hence cardiac after load. In addition to detrimental effects on the heart, elevated central SBP is also thought to be a major determinant of the risk for stroke. Studies have shown that ARBs (irbesartan) reduce cAI whereas atenolol increases it. Furthermore, central to peripheral pulse pressure (PP) amplification is unaffected by treatment with irbesartan, but decreases with atenolol. This could partly explain the reported differential effects of ARB versus β-blocker treatment on cardiovascular mortality in patients with essential hypertension.

**ARBs and Cancer Risk**

A meta-analysis published in Lancet Oncology (2010) raised the possibility that angiotensin receptor blockers (ARBs) might increase the risk of malignancy. This generated a significant debate until the publication of two further meta-analyses, neither of which demonstrated an increased risk of new cancer.
occurrence or cancer-related death with the use of ARBs in patients with hypertension, heart failure, and/or nephropathy. Overall, the bulk of evidence today indicates that ARBs are not associated with increased cancer risk, as endorsed by the FDA.54

Individual Differences Among ARBs
Telmisartan vs. others
Ambulatory blood pressure monitoring (ABPM) has shown that Telmisartan 80 mg confers significantly greater blood pressure lowering than several other ARBs. When compared with Valsartan 160 mg, Telmisartan provided sustained antihypertensive efficacy and superior control of blood pressure during the early morning period.55 3 ABPM studies comparing Telmisartan 40 or 80 mg with losartan 50 or 100 mg demonstrated that Telmisartan provided greater reductions than losartan in both the 24-hour mean SBP and DBP and in the in last 6 hours of the dosing interval.56

ABPM provides more clinical data and is a better predictor of target-organ damage than other BP monitoring methods. Considerable focus was placed on the use of ABPM in the clinical program of Telmisartan, providing the largest ABPM database for a single ARB. Studies using ABPM showed that differences in efficacy and duration of action exist within the ARB class. A meta-analysis of trials using ABPM showed that Telmisartan was the most efficacious and exhibited the longest duration of action.56 In clinical practice, these qualities of ARBs may optimize 24-hour BP control, including the critical early morning period.

References
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15. Neutel JM. Clinical studies of CS-866, the newest angiotensin II receptor antagonist. Am J Cardiol 2001;87:37–43.


