Angiotensin Receptor Blockers and Diuretics as Combination Therapy: Clinical Implications

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Despite the overwhelming evidence that adequate control of blood pressure (BP) significantly reduces cardiovascular morbidity and mortality, only 34% of hypertensive patients in the US have their BP controlled to the recommended goal of <140/90 mm Hg. This number falls short of the Healthy People 2010 goal of 50%, and indicates an urgent need for improved antihypertensive therapy. Furthermore, although BP control rates have improved during the past decade, the prevalence of hypertension is increasing. Thus, there is a persistent need for effective implementation of BP control guidelines in the community.

Regarding the optimal use of antihypertensive therapy, new guidelines provided recently by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) are in agreement with the recommendations that thiazide-type diuretics should be used as initial therapy in most patients. Thiazide diuretics are efficacious and typically more affordable than most other antihypertensive agents. However, less than 50% of hypertensive patients are able to achieve their BP goal with the use of any monotherapy. The JNC 7 has recommended that if BP is >20/10 mm Hg above goal, a second antihypertensive agent from a different drug class should preferably be used in combination with a diuretic. Additional agents include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), β-blockers (BBs), and calcium channel blockers (CCBs).

In addition to achieving target BP goals, antihypertensive therapy should also offer prevention against hypertension-associated complications, such as heart failure, stroke, and kidney disease. Agents that block the renin-angiotensin-aldosterone system (RAAS), ie, ACEIs and ARBs, are particularly effective at lowering BP and providing cardiovascular and renal protective benefits over and beyond their effects on BP.

RAAS Blockade and ARBs

Activation of the RAAS may play a pathogenetic role in hypertension, cardiovascular hypertrophy, large artery stiffness, and atherogenesis. Importance of the RAAS in promoting target-organ disease in hypertension is being increasingly recognized and emphasized. The ACEIs and ARBs block the RAAS through different sites of action, but both drug classes demonstrate protective effects on the heart and kidney.

Unlike ACEIs, which provide incomplete angiotensin II blockade due to alternate pathways of angiotensin II (Ang II) production, ARBs provide a more complete and specific suppression of the RAAS. The ARBs block the binding of Ang II to the angiotensin type I (AT1) receptor, independent of the pathway of Ang II generation. The AT1 receptor blockade results in smooth muscle relaxation; reduction in peripheral vascular resistance, plasma volume, aldosterone secretion and cellular hypertrophy; and increased excretion of water and salt. Although ARBs block the AT1 receptor site, the angiotensin type 2 (AT2) receptor is still free to bind with Ang II. Preliminary data suggest that AT2 receptor activation mediates vasoconstriction, cell growth inhibition, apoptosis, and tissue repair, thereby counteracting some of the pathogenic effects precipitated by the binding of Ang II at the AT1 receptor.

Cough and angioedema may be associated with ACEI therapy due to clinical-mediated effects, but ARBs are unlikely to be associated with these adverse events (rare case reports of angioedema have been documented with the ARB losartan). As a result, ARB usage is associated with greater patient compliance. The incidence of adverse events associated with ARBs in clinical studies is generally similar to and not higher than placebo. The ARBs exert an antihypertensive efficacy similar to other drug classes, including ACEIs, CCBs, diuretics, and β-blockers, with the added benefit of having superior tolerability. In some large-scale studies, ARBs provided remarkable protection against cardiovascular (CV) morbidity and mortality in high-risk patients. As with ACEIs, significant regression of left ventricular hypertrophy has been demonstrated with ARB usage. Like ACEIs, ARBs retain their effectiveness in renal insuf-
ciency, and can thus be recommended for possible reno-

protection. Clinical trials with ARBs have shown a 20% to

30% reduction in the progression of renal damage in type

2 diabetics with nephropathy.20 The ARBs demonstrate

advantageous efficacy and tolerability, and are useful as

first-line antihypertensive agents, especially in high-risk

individuals.

Head-to-head trials show that the newer ARBs—can-
desartan, cilexetil, irbesartan, and telmisartan—demon-
strate significantly better BP reductions than the older

ARBs, losartan potassium, and valsartan. Furthermore,

olmesartan medoxomil, the newest ARB to be approved,

has shown significantly better diastolic BP reductions ver-

tus losartan potassium, valsartan, and irbesartan. Olmes-

tan, like other long-acting ARBs, compares favorably with

other antihypertensive agents, such as atenolol, captorpli,
felodipine, and amlodipine besylate.16

As has been observed with other classes of antihyper-
tensive agents, ARBs as monotherapy generally do not

reduce BP to recommended levels in most hypertensive

individuals,8 hence, combination therapy with a diuretic

significantly enhances the BP-lowering potential of ARBs.

In this issue, a study by Chrysant et al suggests that

olmesartan and hydrochlorothiazide (HCTZ) may be a

potent antihypertensive combination.21

**ARB/HCTZ Combination Therapy and Hypertension Control**

An analysis of 17 randomized, controlled clinical trials

evaluated the antihypertensive efficacy of losartan potas-

sium, valsartan, irbesartan, and candesartan in combina-

tion with HCTZ.22 The combination of these ARBs with

12.5 mg/d (HCTZ) resulted in a reduction in diastolic BP

of 9.9 to 13.6 mm Hg and in systolic BP of 16.1 to 20.6

mm Hg. Responder rates were 56% to 70%.

In comparison, pooled data from seven placebo-con-

trolled trials designed to evaluate the antihypertensive

efficacy of the new ARB, olmesartan monotherapy, showed

mean reductions in seated (Se) diastolic BP and Se

cydiastolic BP of 12.2 and 15.1 mm Hg, respectively, at the

recommended starting dosage of 20 mg/d. At the maxi-

mum recommended dosage of 40 mg/d,8,15 olmesartan

dmedoxomil monotherapy showed mean reductions in Se

cydiastolic BP and Se systolic BP of 13.1 and 17.6 mm Hg,

respectively. Therefore, olmesartan monotherapy is asso-

ciated with significant decreases in diastolic BP and sys-

tolic BP levels, similar to those observed for other ARBs

when used in conjunction with HCTZ.

The factorial design clinical study reported by Chrysant

et al was the first to evaluate the antihypertensive efficacy

of olmesartan in combination with HCTZ.21 This particu-

lar study design was chosen because trials of this type are

typically used to evaluate whether a specific ARB/HCTZ

combination therapy is more efficacious than either of the

individual agents used as monotherapies. These trials are

not intended to evaluate a dose–response relationship be-
tween different dose combinations, but rather are statisti-
cally powered to evaluate the safe and effective clinical
doses of ARB/HCTZ combination therapy in hypertensive

patients. In the Chrysant et al study, a total of 502 patients

were randomized to one of 12 groups for 8 weeks of

treatment of placebo, olmesartan monotherapy (10, 20, or

40 mg/d), HCTZ monotherapy (12.5 or 25 mg/d), or

combination therapy with olmesartan plus HCTZ.

Olmesartan plus HCTZ demonstrated a dose-related
efficacy across all combinations evaluated that were

greater than monotherapy with either agent. The reduc-
tions from baseline in mean trough Se diastolic BP/Se

cydiastolic BP ranged from 16.4/20.1 mm Hg for the olme-
sartan 20 mg/HCTZ 12.5 mg combination up to 21.9/26.8

mm Hg for the olmesartan 40 mg/HCTZ 25 mg combina-
tion. The responder rate ranged from 77.1% to 81.0% of

patients in the olmesartan HCTZ 12.5 mg/d combination

groups, and from 89.1% to 92.3% of patients in the olme-
sartan HCTZ 25.0 mg/d combination groups. Thus, com-

bining olmesartan with a diuretic resulted in significantly

greater reductions in systolic BP and diastolic BP than

either agent alone.

Optimal use of an ARB with a diuretic follows the

recommended therapeutic strategy of combining two an-
thypertensive agents, with complementary mechanisms of

action to obtain a greater BP reduction. Combining an

ARB with a diuretic has several advantages, including: 1)

allowing lower doses of component drugs to be used than

would be required to achieve the same efficacy using a

single agent, thereby resulting in lower incidence of ad-

verse effects, and improved patient compliance; 2) poten-
tiation of the antihypertensive and hemodynamic response

of ARBs, resulting from salt depletion induced by thiazide
diuretics; and 3) reducing the risk of diuretic-induced

hypokalemia.

By virtue of their pharmacologic actions, thiazide di-

uretics can cause hypokalemia in some patients. In sus-

ceptible patients, diuretic-induced hypokalemia can trigger

cardiac arrhythmias. Furthermore, it has been proposed

that the hypokalemia may predispose patients who have

silent myocardial ischemia to potentially fatal arrhyth-

mias.23 Hypokalemia caused by hydrochlorothiazide has

also been implicated in the development of rhabdomyol-
ysis.24 The HCTZ-induced hypokalemia has been shown

to be less prevalent in clinical studies when HCTZ is

combined with an ARB.21,25–27 One explanation for di-

uretic-induced hypokalemia is activation of the renin-an-
giotensin-aldosterone axis. The ARBs interrupt the renin-

aldosterone link normally mediated by Ang II and, there-

fore, aldosterone-induced urinary potassium loss is

attenuated. Recent observations suggest that for patients

with diuretic-induced hypokalemia, it may be beneficial to

reduce the HCTZ and add an ARB to maintain normal

potassium homeostasis. In this way, adequate BP control

can be achieved without the risk of hypokalemia associ-

ated with the high-dose HCTZ therapy.27
Conclusions

There is little doubt that lowering the BP level to any degree in patients with hypertension reduces the risk of stroke and ischemic heart disease. The health benefits are far greater when the BP is normalized. In addition to nonpharmacologic therapy, drug treatment is often necessary to achieve goal BP levels. It is now clearly recognized that adequate BP reduction cannot be achieved with monotherapy. Thus, the current guidelines recommend liberal utilization of combination therapy to achieve desired BP levels.

Combination therapy can include the addition of a second agent to an existing monotherapy regimen or the concurrent use of multiple drugs of fixed combination products. Whichever option is used, the dosages should be properly titrated based on the therapeutic response and maintenance of achieved BP levels. Antihypertensive drugs from different pharmacologic classes can be combined to capture effective BP control rates. A common (and often required) component of combination antihypertensive therapy is a thiazide diuretic. When a thiazide is added to any nondiuretic antihypertensive drug, one can expect a synergistic, or sometimes an additive, effect on the BP. Hence, antihypertensive combinations, which include a thiazide diuretic, have been widely and successfully used in clinical practice for many decades. This is a well-tested, time-honored strategy.

Although the concept of combination therapy is not new, it is only in the recent years that the interest in the approach has resurfaced. Data from large therapeutic and end point trials in hypertension conducted in the past 10 to 15 years has convinced us that to decrease morbidity and mortality in hypertension, a majority of patients require more than one drug, at least two, and in some cases three. Fixed dose combinations that include a diuretic have been available for many years. For example, thiazide/β-blocker, thiazide/centrally acting agent, and thiazide/ACEI combination formulations have been successfully used in clinical practice. However, it is only recently that fixed dose combinations of long-acting ARBs and diuretics have become available, and are being increasingly used in the management of hypertension with much clinical success. Based on their pharmacodynamic, pharmacokinetic, clinical, and biochemical effects (Table 1), combination of an ARB with a thiazide diuretic yields a significant therapeutic benefit in achieving improved control of hypertension in the community, while providing target organ protection and freedom of side effects, which historically limited the widespread acceptance of previously available combination therapies. Because a large number of patients treated for hypertension continue to have high BP, there is a general agreement to initiate therapy with the combination of two agents from different pharmacologic classes—a strategy recommended by JNC 7 to improve the BP control rates in the community.

### Table 1. Clinical consequences of ARBs and diuretics

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<th>ARBs</th>
<th>Diuretics</th>
<th>ARBs + Diuretics</th>
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<tbody>
<tr>
<td>Antihypertensive effects</td>
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<tr>
<td>Renin-angiotensin system</td>
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<td>=</td>
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<tr>
<td>Left ventricular hypertrophy</td>
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References

15. Neutel JM: Clinical studies of CS-866, the newest angiotensin II receptor antagonist. Am J Cardiol 19 2001;87:37C–43C.