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ORIGINAL ARTICLE

Angiotensin-receptor blockers and diuretics—Advantages of combination

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Abstract
Surveys have shown that in as many as half of patients treated for hypertension, blood pressure (BP) is not controlled to target levels; many more persons have undertreated hypertension. Uncontrolled hypertension is a serious risk factor for cardiovascular events such as stroke, heart failure, myocardial infarction and target-organ disease. Studies have shown that strict BP control significantly reduces the occurrence of these cardiovascular outcomes; however, in the majority of patients, effective BP control requires two or more antihypertensive agents. The combination of an angiotensin-receptor blocker (ARB) and a thiazide diuretic is appealing, since these agents have complimentary effects on BP reduction, left ventricular hypertrophy and progression of renal disease. In addition, this combination provides excellent tolerability. The combination of an ARB and a thiazide diuretic may be of particular value in patient populations who tend to have poor BP control on monotherapy, or have additional cardiovascular or renal risk factors.

Key Words: *Angiotensin-receptor blocker, combination therapy, diuretic, hypertension, populations*

Introduction

Hypertension is a highly prevalent condition: a recent report estimated that 28% of the North American population 35–64 years of age has hypertension (BP > 140/90 mmHg) (1). In many European countries, the rate is higher, reaching 55% in Germany for persons in the same age range. Moreover, targets for blood pressure (BP) control are met in less than one-quarter of persons with hypertension (1). The EUROASPIRE II survey found that only 49% of patients treated for hypertension achieved their goal BP, while the equivalent rate in the USA is only 53% (2,3). Moreover, data from the Framingham Heart Study showed that 49.5% of patients over 65 years with BP of 130–139/85–89 mmHg progressed to hypertension in 4 years, and an individual who is normotensive at age 55 years has a 90% lifetime risk of developing hypertension (4,5).

Controlling hypertension is of paramount importance for the prevention of cardiovascular morbidity and mortality, particularly in patients with other risk factors. The European Society of Hypertension (ESH)/European Society of Cardiology (ESC) 2003 guidelines and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) set the target for BP control in most hypertensive patients at $<140/90$ mmHg or $<130/80$ mmHg for most patients with concomitant diabetes or chronic kidney disease (6,7). Lifestyle modifications (such as weight loss, and reducing saturated fat and sodium intake) are recommended for patients with BP $\geqslant 120/80$ mmHg (5,7).

In the majority of hypertensive patients, lifestyle modification plus monotherapy is insufficient to achieve BP goals. Numerous major trials demonstrated that combination therapy is frequently necessary (8–13). In the 1998 Health Survey for

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England, however, 60% of patients who were receiving antihypertensive treatment received only one agent (14).

The utility of diuretics in the prevention of cardiovascular complications has been shown in major clinical trials, and these agents have a long history of safety and efficacy (10,15). The JNC 7 guidelines recommend that drug treatment for most patients include a thiazide diuretic, while the ESH/ESC guidelines note that thiazides are appropriate for many patients with hypertension (6,7). In some patients, though, hypertension is resistant to diuretic treatment. This resistance is related to activation of the renin–angiotensin–aldosterone system (RAAS), which is caused by an excessive increase in circulating renin (16).

The RAAS plays a significant role in the regulation of BP and target-organ damage. Angiotensin II is a key component of the RAAS, and most deleterious effects are mediated by the angiotensin II type 1 receptor (AT_1). Since angiotensin II is also synthesized in some tissues via pathways that bypass angiotensin-converting enzyme (ACE), such as chymase, inhibition of the AT_1 receptor by angiotensin-receptor blockers (ARBs) may result in a more complete RAAS blockade than offered by ACE inhibition (17). Moreover, ARBs are associated with excellent tolerability and have benefits beyond BP lowering, such as the reduction of left ventricular hypertrophy and renoprotection (13,18–20).

The combination of an ARB with a thiazide diuretic has been shown to be efficacious and well tolerated in numerous clinical trials (11–13,21). This combination could be of particular value in hypertensive patients with additional cardiovascular risk factors or in populations whose BP is traditionally poorly controlled, such as elderly persons, persons with diabetes mellitus and black patients. Fixed-dose combinations may be particularly appealing because they also simplify treatment regimens and appear likely to improve patient compliance.

Does ARB plus diuretic add "VALUE"?

The recently reported Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial compared treatment regimens based on the calcium-channel blocker (CCB) amlodipine (5–10 mg) with valsartan (80–160 mg [the then-approved dosage range for hypertension]) in 15,245 high-risk hypertensive patients (11). In both arms, step-up treatment included hydrochlorothiazide (HCTZ) 12.5–25 mg, which was the sole add-on treatment for 24.6% of patients in the ARB arm and 23.8% in the CCB arm. The trial reported no difference in the primary outcome of combined cardiac morbidity and mortality ($p=0.49$), despite a difference in BP control favoring the CCB.

One key result of the VALUE trial is the recognition of the importance of swift titration to achieve BP target levels. The BP and end point differentials were widest (BP up to 4.0/2.1 mmHg lower in the amlodipine arm) during the titration phase of the trial (0–6 months), while the differences were much smaller (BP=1.8/1.5 mmHg lower in the amlodipine arm) at the end of the study. Indeed, it might be reasonable to conclude that the narrowing gap implies that the titration schedule, rather than any intrinsic quality of the study medications, was the most crucial variable in the between-group disparity (11).

Moreover, if BP control is the sole determinant of morbidity and mortality, why did the arm with the greatest BP reduction not show significantly greater benefit? One possible explanation is that the ARB-based regimen provided a benefit in addition to BP-lowering efficacy. This hypothesis is supported by a temporal review (that correlates differences in primary and secondary end-point rates with the differences in BP between arms) (Figure 1) (11). Moreover, a post-hoc analysis using serial median matching found a significant heart-failure benefit with valsartan (19% reduction [95% confidence interval, CI, 1–34%; $p=0.04$]) and a trend in the composite end point favoring the ARB (22). In addition, there was a significant 23% reduction (95% CI 14–31%) in new-onset diabetes with valsartan ($p<0.0001$) (11).

Ultimately, the message of VALUE may be that, despite the potential advantages of ARB treatment, rapidly reaching target BP may be a crucial determinant of morbidity and mortality for high-risk patients with hypertension and should be a focus of treatment. If this is the case, combination therapy, which most patients ultimately require, could be more advantageous than monotherapy in helping patients get to goal quickly.

ARBs/diuretics in special populations

Elderly patients

It is estimated that approximately three-quarters of people over age 70 years have hypertension (7). Furthermore, persons over 60 years have a high rate of isolated systolic hypertension (approximately 15%) (23), which is more predictive of coronary

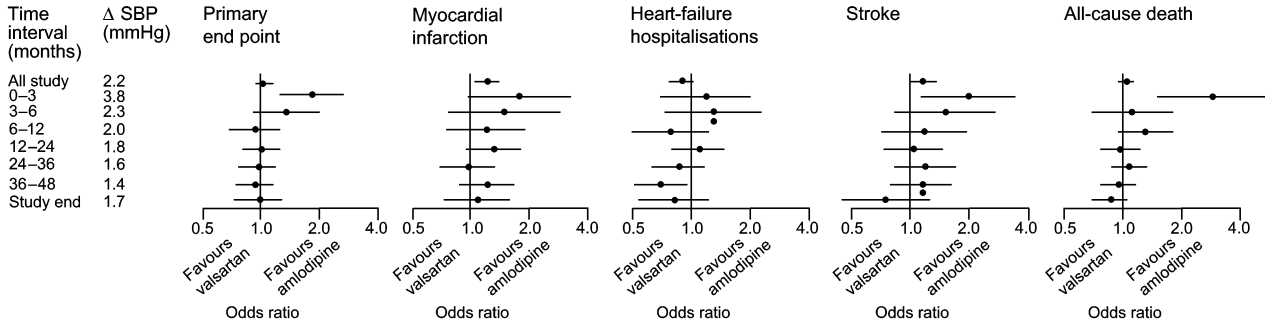

Figure 1. Differences in blood pressure between treatment groups with odds ratios for primary end point, secondary end points, and all-cause death during consecutive time periods in the VALUE trial (11).

heart disease in patients over age 50 years than diastolic BP (24).

Elderly hypertensive patients, with or without isolated systolic hypertension, have an elevated risk of cardiovascular complications, including heart failure, stroke and dementia (25). Though elevated systolic BP is most common among elderly patients, BP control rates are the lowest in this age group (26,27).

Combining an ARB with a diuretic may be especially helpful in older patients. It has been theorized that since elderly patients tend to have lower renin levels than younger patients, their BP may tend to be less responsive to agents that directly affect the RAAS (28). This reduced response is not apparent with an ARB/diuretic combination. In the Study on Cognition and Prognosis in the Elderly (SCOPE), ARB-based treatment (candesartan) reduced the incidence of non-fatal stroke by 27.8% (95% CI, 18–50%; $p=0.04$) vs background therapy (12). Diuretics were combined with the ARB in 33% of patients (mean age 76.4 years). In a substudy of the Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial, patients with isolated systolic hypertension and left ventricular hypertrophy showed that losartan-based treatment (58.8% of patients received diuretic add-on treatment) reduced the risk of the combined end point of cardiovascular death, stroke or myocardial infarction by 25% (95% CI 1–44%; $p=0.06$) compared with atenolol (49.2% of patients received add-on diuretic therapy) (19). In addition, losartan reduced electrocardiographic left ventricular hypertrophy significantly more than atenolol ($p<0.001$) and was better tolerated (19).

Fixed combination treatment has demonstrated increased efficacy in older patients compared with ARB monotherapy. Valsartan plus HCTZ was investigated in elderly non-responders to valsartan monotherapy. Mean changes from baseline in BP at 8 weeks are shown in Figure 2(29). The response rate, defined as a mean sitting diastolic

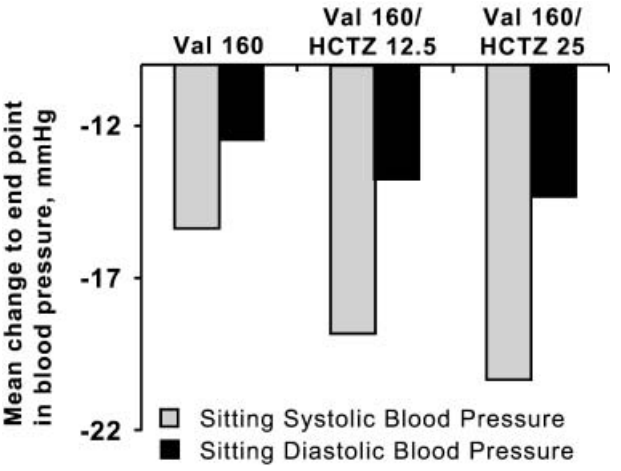

Figure 2. Treatment of elderly patients (>65 years) not adequately controlled (defined as mean diastolic blood pressure ≥95 and ≤110 mmHg for patients taking valsartan 160 mg monotherapy once daily over a 4-week period) with valsartan monotherapy (29). BP, blood pressure; HCTZ, hydrochlorothiazide; SDBP, sitting diastolic blood pressure; SSBP, sitting systolic blood pressure; Val, valsartan.

BP<90 mmHg or decrease in mean sitting diastolic BP>10 mmHg at the end of treatment, was 71% with valsartan 160 mg plus HCTZ 25 mg. In addition, the tolerability of the combination was good and did not differ from monotherapy (29). Excellent tolerability of this combination was also demonstrated in another study of patients aged 60–80 years with isolated systolic hypertension. For equipotent BP lowering, valsartan, alone or in combination with HCTZ was significantly better tolerated than amlodipine-based treatment ($p<0.003$) (30).

Patients with diabetes mellitus or insulin resistance

Persons with type 2 diabetes mellitus, particularly younger persons, have an increased prevalence of hypertension: approximately 40% of persons aged

45 years and 60% of persons aged 75 years (9). Hypertension compounds the risk of cardiovascular and kidney disease faced by patients with diabetes (31). Therefore, the ESH/ESC, JNC and the American Diabetes Association guidelines generally set the BP target for patients with diabetes at $<130/80$ mmHg (6,7,32). The guidelines acknowledge that two or more agents are often required to attain this target and note the benefits of RAAS blockade in these patients (6,7,32).

Hypertension and microalbuminuria are risk factors for cardiovascular events and progression of kidney disease in diabetic patients (18,33). ARBs have demonstrated renoprotective properties in addition to their BP-lowering effect. In the 2-year Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria study (IRMA 2), irbesartan (300 mg) demonstrated a 70% reduction in the risk of development of clinical diabetic nephropathy compared with placebo (95% CI 39–86%; $p<0.001$) (18). In the Irbesartan Diabetic Nephropathy Trial (IDNT), irbesartan 300 mg showed a 23% reduction (95% CI 17–37%; $p=0.006$) in the occurrence of the primary composite end point (doubling of the baseline serum creatinine concentration, development of end-stage renal disease or all-cause mortality) when compared with amlodipine 10 mg or background therapy (20% risk reduction [95% CI 3–34%]; $p=0.02$) in patients with type 2 diabetes and nephropathy (34). Patients in this study received an average of three antihypertensive medications (34). The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial showed that a losartan-based (50–100 mg) multidrug regimen resulted in a 16% risk reduction (95% CI 2–28%) in the same composite end point compared with background treatment ($p=0.02$) among hypertensive patients with diabetic nephropathy (33). In patients with type 2 diabetes and microalbuminuria, with or without hypertension, the MicroAlbuminuria Reduction with VALsartan (MARVAL) study showed that valsartan (80–160 mg) reduced microalbuminuria levels 44% compared with 8% for amlodipine (5–10 mg; $p<0.001$) (35). Reversion from microalbuminuria to normoalbuminuria was twice as great for valsartan compared with amlodipine (30% vs 15%; $p=0.001$), although BP lowering was similar in the two treatment groups. About half of patients in both treatment arms received add-on thiazide diuretic, and a quarter received an α-blocker (35).

Clinical-trial data also show an intriguing and potentially important interaction between ARB use and a reduction in new-onset diabetes. In LIFE, treatment with losartan was associated with a 25% reduction in new cases of diabetes vs atenolol ($p<0.001$), perhaps due to a differential effect on insulin resistance (13). Further, the 23% reduction in new-onset diabetes with valsartan that was shown in VALUE is particularly striking. CCBs are believed to be metabolically neutral, which implies that valsartan treatment is metabolically beneficial. Moreover, recent reports find that new-onset diabetes carries similar long-term risk similar to that of pre-existing diabetes (36,37).

Black patients

The prevalence of hypertension is elevated in some black populations (38,39). Studies have shown that blacks with hypertension also have a higher prevalence of left ventricular hypertrophy, which is a powerful independent predictor of cardiovascular events (38). The consensus statement of the Hypertension in African Americans Working Group of the International Society on Hypertension in Blacks recommends combination therapy as first-line antihypertensive treatment for black patients whose BP is above the target by 15 mmHg systolic or 10 mmHg diastolic (40).

One study examined the effect of adding either an ACE inhibitor or a diuretic to valsartan monotherapy in hypertensive black patients maintained on a high-salt diet (200 mEq Na^+/day) (41). Compared with valsartan 160 mg alone, valsartan plus HCTZ (160 mg/12.5 mg) caused a greater reduction in BP ($-10.5/-6.9$ mmHg; $p<0.01$) than valsartan plus the ACE inhibitor benazepril (160 mg/20mg; $+2.4/-1.7$ mmHg; p=not significant) or valsartan 320 mg ($-3.8/-3.3$ mmHg; p=not significant). In this population, the efficacy of valsartan was only slightly affected by high salt intake (41).

The consensus statement of the Hypertension in African Americans Working Group also stresses the importance of selecting the appropriate antihypertensive agent to protect against target organ damage (40). BP reduction can slow the progression of renal disease, which is particularly important for black patients since they are three to four times more likely to develop end-stage renal disease than white patients (42). The African American Study of Kidney Disease (AASK), which was conducted in black patients with hypertensive kidney disease, showed that a ramipril-based regimen (2.5–10 mg) reduced the clinical composite outcome (reduction in glomerular filtration rate by $\geqslant 50\%$, end-stage renal disease or death) by 22% (95% CI 1–38%; $p=0.04$) and 38% (95% CI 14–56%; $p=0.004$) vs

metoprolol-based (50–200 mg) and amlodipine-based (5–10 mg) regimens, respectively (43).

Conclusions

There has been a paradigm shift in the treatment of hypertension away from BP as the sole consideration toward cardiovascular protection. For the majority of patients, adequate BP control and target organ protection can only be reached using multiple antihypertensive agents (6,7). The combination of an ARB with a thiazide diuretic offers effective BP lowering coupled with improvements in left ventricular hypertrophy, renal function and reduction of new-onset diabetes.

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