Fixed combination of losartan and hydrochlorothiazide and reduction of risk of stroke

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Abstract: A fixed-dose combination of losartan/hydrochlorothiazide (HCTZ) therapy may be a logical choice for antihypertensive treatment, including for initial therapy in patients with blood pressure elevation >20/10 mmHg above treatment target. The renin–angiotensin–aldosterone–system-activating effect of hydrochlorothiazide augments the efficacy of blocking the angiotensin II type 1 (AT_1) receptor with losartan. Some adverse effects associated with hydrochlorothiazide, including increased risk for new-onset diabetes mellitus, may be offset by losartan. Losartan was frequently administered with hydrochlorothiazide in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, in which there was a 25% risk reduction for stroke in the losartan-based compared with the atenolol-based treatment group. The efficacy, tolerability, and convenience of losartan/HCTZ combination therapy may increase patient compliance and lower risk for stroke, a devastating outcome in patients with hypertension.

Keywords: angiotensin receptor blocker, combination therapy, hydrochlorothiazide, hypertension, stroke

Introduction to management of stroke risk in hypertension

Stroke has enormous consequences for patients and healthcare systems worldwide (Goldstein et al 2006). Stroke has been reported to be the most common cardiovascular outcome in many (Kjeldsen et al 2001), but not all (ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group 2002), hypertension clinical trials. Stroke is the third leading cause of death in the US, with a yearly incidence of 700,000 in 2004 and a 1-month fatality rate of about 12% (Rosamond et al 2007). Approximately one third of survivors of stroke who have lived for at least 6 months post-stroke are dependent on others for activities of daily living (Warlow 1998). The estimated direct and indirect cost of stroke in the US in 2007 is US$62.7 billion (Rosamond et al 2007).

The predominant modifiable risk factor for stroke is hypertension (Wolf et al 1991; Straus et al 2002). Data from the National Health and Nutrition Examination Survey for 1999–2000 (NHANES, n = 4531) showed that the prevalence of hypertension in the US is increasing (Fields et al 2004). In 1999–2000, 31.3% of the NHANES population had hypertension (blood pressure ≥140/90 mmHg or treated with antihypertensive therapy) (Fields et al 2004), an increase from the 23.4% prevalence reported for 1989–1994 (Wolz et al 2000). This trend was attributed to increased obesity and an aging population (Fields et al 2004). In a report from the 1999–2000 NHANES population (n = 5448), 58.4% of the participants were treated (an increase of 6.0% from 1988–1991), and hypertension was controlled in 31.0% (an increase of 6.4% from 1988–1991) (Hajjar and Kotchen 2003). In European countries, the age- and

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sex-adjusted prevalence of hypertension (≥140/90 mmHg) is 44.2% (vs 27.6% in North America), with an average of 8% of patients with controlled hypertension (vs 23% in North America) (Wolf-Maier et al 2003).

Current guidelines recommend treatment goals of less than 140/90 mmHg for patients with uncomplicated hypertension and less than 130/80 mmHg for patients with diabetes, cardiac disease, or chronic kidney disease (Guidelines Committee 2003; Chobanian et al 2003). In clinical trials (ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group 2002) and clinical practice (Amer 2002), most patients require at least two medications to achieve goal blood pressure. Treatment guidelines for hypertension suggest the use of low-dose combination agents for the initial treatment of hypertension in some circumstances, such as blood pressure elevation greater than 20/10 mmHg over goal (Guidelines Committee 2003; Chobanian et al 2003).

Here we review the stroke results and losartan plus hydrochlorothiazide (HCTZ) use from the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study and discuss the potential advantages of fixed-dose losartan/HCTZ therapy for stroke risk reduction.

The LIFE study

Thiazide diuretics and beta-blockers reduce stroke risk in patients with hypertension (Mulrow et al 2000; Psaty et al 2003). In the LIFE study, 9193 patients aged 55–80 with hypertension (160–200/95–110 mmHg) and electrocardiographic left ventricular hypertrophy were treated for a mean duration of 4.8 years with diuretics for 72% of the time in the losartan group and 70% of the time in the atenolol group (mean dose of HCTZ in each group was 20 mg) (Dahlöf et al 1997, 1998, 2004). An independent Endpoint Classification Committee adjudicated endpoints. Stroke (a component of the primary composite endpoint that also included cardiovascular death and myocardial infarction) was defined as a new-onset neurologic deficit of vascular origin lasting ≥24 hours or until death (Kizer et al 2005). Stroke classification was based on categories developed in the Framingham Study (Wolf et al 1992). Ischemic stroke was assigned in the absence of evidence of primary intracranial bleeding, whereas hemorrhagic stroke required evidence of hemorrhage (ie, bloody spinal fluid and/or blood on computed tomography), excluding cases of vessel rupture due to traumatic, neoplastic, or infectious processes. Ischemic stroke was further classified as embolic or athero-thrombotic. The diagnosis of embolic stroke was based on the presence of a source of embolus (eg, chronic or paroxysmal atrial fibrillation, rheumatic mitral stenosis, recent myocardial infarction, prosthetic heart valve, ulcerated carotid plaque) and consistent clinical features (eg, rapid onset and partial clearing, slightly bloody spinal fluid) or the occurrence of associated peripheral emboli. Atherothrombotic stroke was assigned when no evidence of an embolic etiology was present. Strokes for which a distinct etiology could not be ascertained were classified as other. Neurologic deficits were classified as depression of consciousness, disturbance of vision, paresis or paralysis of one or more extremities, sensory impairment, speech impairment, central cranial nerve dysfunction, memory defect, ataxia, and movement disorder.

The primary composite endpoint of cardiovascular death, stroke, or myocardial infarction was reduced by 13% ($p = 0.021$) in the losartan group, due primarily to a 25% reduction ($p = 0.001$) in stroke. Kizer et al (2005) examined the stroke results in the LIFE study in detail (Table 1). Losartan-based compared with atenolol-based treatment significantly lowered the risk of fatal stroke by 35% (hazard ratio [HR] = 0.65, 95% confidence interval [CI] 0.43–0.96, $p = 0.032$) and of atherothrombotic stroke by 27% (HR = 0.73, 95% CI 0.60–0.89, $p = 0.002$). The risk reductions for hemorrhagic and embolic stroke were 20% and 24%, respectively, but these were not statistically significant, possibly due to low numbers. The effect of losartan-based therapy on stroke incidence was independent of degree of electrocardiographic left ventricular hypertrophy, Framingham risk score, systolic blood pressure during follow-up, prevalent and incident atrial fibrillation or coronary heart disease, and treatment with aspirin, warfarin, or statins. The risk of recurrent stroke was significantly reduced in the losartan compared with the atenolol group (26 versus 46 patients with ≥2 incident strokes, $p = 0.017$) despite comparable use of antiplatelet and/or anticoagulant medications 30 days after the first stroke by 78% of patients in both groups. The number of neurologic deficits per stroke was similar in both treatment groups, but there were fewer strokes in the losartan group for virtually every level of stroke severity. The number needed to treat for 5 years to prevent one stroke in the losartan group as a whole was 54. The numbers needed to treat for 5 years to prevent one stroke for patients with cerebrovascular disease, isolated systolic hypertension, and atrial fibrillation who were treated with losartan were 25, 24, and 9, respectively.

Among black patients, greater stroke risk was observed in the losartan-based compared with the atenolol-based treatment group, which approached statistical significance

Table 1 Stroke subtypes by treatment in the LIFE study

Stroke type	Losartan (n = 4605)		Atenolol (n = 4588)		Adjusted[b] hazard ratio (95% CI)	p-value	Unadjusted hazard ratio (95% CI)	p-value
	n (%)	Rate[a]	n (%)	Rate[a]				
Any stroke	232 (5.0)	10.8	309 (6.7)	14.5	0.75 (0.63–0.89)	0.001	0.74 (0.63–0.88)	<0.001
Ischemic	203 (4.4)	9.2	277 (6.0)	12.6	0.73 (0.61–0.88)	0.001	0.73 (0.61–0.87)	<0.001
Athero-thrombotic	170 (3.7)	7.9	233 (5.1)	10.9	0.73 (0.60–0.89)	0.002	0.72 (0.59–0.88)	0.001
Embolic	36 (0.8)	1.6	48 (1.0)	2.2	0.76 (0.50–1.18)	0.22	0.75 (0.48–1.15)	0.19
Hemorrhagic	27 (0.6)	1.2	34 (0.7)	1.6	0.80 (0.48–1.32)	0.38	0.79 (0.48–1.31)	0.36
Other/Unclassified	5 (0.1)	0.2	5 (0.1)	0.2	1.02 (0.30–3.53)	0.97	1.00 (0.29–3.44)	0.99
Any fatal stroke	40 (0.9)	1.8	62 (1.4)	2.8	0.65 (0.43–0.96)	0.032	0.64 (0.43–0.95)	0.028

[a]Per 1000 patient-years of follow-up.

[b]For degree of left ventricular hypertrophy and Framingham risk score at randomization.

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Abbreviations: CI, confidence interval.

(unadjusted HR = 1.99, 95% CI 1.00–3.98, p = 0.051) (Julius et al 2004a; Kizer et al 2005). Many American blacks appear to have low-renin, salt-sensitive hypertension (Wright 1988) and respond less to renin–angiotensin–aldosterone–system (RAAS) antihypertensive agents (Hall 1987). However, losartan-based and atenolol-based therapy resulted in comparable blood-pressure lowering in black and non-black subgroups in the LIFE study, and losartan was associated with greater left ventricular hypertrophy regression than was atenolol in both black and non-black patients (Julius et al 2004a). Adjustment for racial differences in baseline characteristics did not affect the endpoint results, and changes in laboratory measures during the trial were similar in the black and non-black subgroups (Julius et al 2004a). Thus, there is no apparent explanation for the endpoint results in black patients in the LIFE study (Julius et al 2004a).

Discussion

As early as 1993, it was shown that treatment with losartan at doses that did not affect systolic blood pressure decreased the risk of stroke in stroke-prone spontaneously hypertensive rats, suggesting that angiotensin II affects the pathophysiology of stroke and that losartan has a direct stroke benefit that is independent of blood pressure reduction (Stier et al 1993). These findings were tested in humans in the large, well-conducted LIFE study in which losartan-based antihypertensive therapy significantly decreased risk for stroke when compared with atenolol-based therapy in the context of comparable blood pressure reductions in both treatment groups (Dahlöf et al 2002). Several potential mechanisms that may be responsible for the beneficial effect of losartan in the LIFE study have been suggested (Dahlöf et al 2002; Mancia 2004; Devereux and Dahlöf 2007a): attenuation of arterial stiffness; inhibition of angiotensin II-induced endothelial dysfunction (Schiffrin et al 2000); inhibition of hypertrophy, fibrosis, and remodeling of cerebral arteries; beneficial effects on concomitant risk factors (albuminuria [Ibsen et al 2004], left ventricular hypertrophy [Devereux et al 2004; Kizer and Devereux 2006; Okin et al 2003], atrial fibrillation [Wachtell et al 2005], new-onset diabetes [Lindholm et al 2002]); inhibition of platelet aggregation; unique molecule-specific effects (eg, uric acid [Hoieggen et al 2004]); metabolite-specific anti-inflammatory activity; and neuro-protective effects (Sadoshima 2002).

Many patients require more than one antihypertensive agent for blood pressure control (ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group 2002; Amer 2002). Very frequently this includes HCTZ because of its antihypertensive efficacy, beneficial effects on stroke (Mulrow et al 2000; Psaty et al 2003), and low cost (Chobanian et al 2003). Combining two antihypertensive agents, such as HCTZ and an angiotensin receptor blocker (ARB), usually produces additive antihypertensive effects. In a meta-analysis of ARB monotherapy and combination therapy with HCTZ (Conlin et al 2000), decreases in systolic and diastolic blood pressures were comparable for the therapies studied (candesartan, irbesartan, losartan, valsartan). The antihypertensive efficacy of losartan plus HCTZ has been demonstrated in studies of initial/first-line use (Gradman et al 2002; Salerno et al 2004), in patients with inadequate blood pressure lowering with losartan monotherapy (Gleim et al 2006), and in the LIFE study (Devereux et al 2007). A fixed-dose combination of losartan/HCTZ therapy may be a logical choice for initial therapy in patients with blood pressure elevation >20/10 mmHg above treatment

target (Chobanian et al 2003); this is the only fixed-dose combination therapy currently approved in the US for the treatment of severe hypertension.

Fixed-dose combinations of HCTZ with ARBs or angiotensin-converting enzyme inhibitors (ACEIs) have enhanced tolerability (Kjeldsen et al 2005a; Waeber 2003). Thiazide diuretics are most effective in patients who have salt- or volume-sensitive hypertension. Most patients respond to the salt depletion and volume contraction induced by a thiazide diuretic by releasing renin (Sassano et al 1989). Blood pressure is then more dependent on angiotensin II, and the blood pressure effect of diuretics is blunted. Addition of an agent that inhibits the RAAS further decreases blood pressure and generally has an additive antihypertensive effect. In order for any drug that blocks the RAAS to work optimally, high background activity of the system is necessary, a situation not typical in salt-sensitive hypertension and one that is enhanced by treatment with thiazide diuretics (Brunner et al 1980; Sassano et al 1989) and/or a low-salt diet (Anderson and Morgan 1990; MacGregor et al 1987; Navis et al 1987; Singer et al 1995).

There may be better tolerability with a 2-drug combination of higher doses of ARB/HCTZ compared with a multi-drug regimen of lower doses of less well-tolerated antihypertensive agents, leading to better patient compliance. Many of the undesirable side-effects of thiazide diuretics may be lessened by combination with a RAAS agent (Table 2). Most importantly, the tendency for thiazides to increase the risk for new-onset diabetes during long-term treatment may be offset by RAAS antihypertensive agents. Reductions in new-onset diabetes with ARBs have been noted with candesartan-based versus placebo-based therapy in the Study on Cognition and Prognosis in the Elderly (SCOPE) (Lithell et al 2003), losartan-based versus atenolol-based therapy in the LIFE study (Dahlöf et al 2002), and valsartan-based versus amlodipine-based therapy in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study (Julius et al 2004b). Reductions in new-onset diabetes with ACEIs have been noted with captopril versus diuretics and/or beta-blockers in the Captopril Prevention Project (CAPPP) (Hansson et al 1999) and ramipril versus placebo therapy in the Heart Outcomes Prevention Evaluation (HOPE) study (The Heart Outcomes Prevention Evaluation Study Investigators 2000).

Table 2 Actions of angiotensin receptor blockers and diuretics

	ARBs	Diuretics	ARBs+ Diuretics
Antihypertensive effects	↓	↓	↓↓
Renin-angiotensin system	↓↓	↑	↓
Sympathetic nervous system	↓↓	↑	↓
Potassium balance	↑	↓	=
Uric acid	↓ =	↑	=
Left ventricular hypertrophy	↓↓	↓ =	↓↓

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Abbreviations: ARB, angiotensin receptor blocker

Because of the tendency of RAAS antihypertensive agents to increase serum potassium, hypokalemia is likely to be less of a problem with diuretics when they are combined with RAAS agents (Weinberger 1985). The ARB candesartan did not produce the unfavorable lipid changes of HCTZ administered with or without beta-blocker therapy in the Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation (ALPINE) study (Lindholm et al 2003). A unique quality of one ARB, losartan, is that it lowers serum uric acid (Elliott et al 2001). The increase in uric acid that was noted over the course of the LIFE study, perhaps partially due to concomitant HCTZ treatment, was ameliorated in the losartan-treated group (Hoieggen et al 2004). This appeared to explain 29% of the beneficial treatment effect of losartan on the primary composite endpoint of cardiovascular death, stroke, and myocardial infarction, raising the possibility that some of the beneficial effects of losartan in the LIFE study may not be generalizable to the ARB class. Uric acid level was an independent predictor of stroke in the LIFE study (Kizer et al 2004).

Reducing pill burden has been shown to enhance patients' quality of life and satisfaction and acceptability, adherence, and uptake of medications (Dezii 2000; Wald and Law 2003; Chapman et al 2005; Sleight et al 2006). Increasing patient compliance with antihypertensive therapy is particularly important in patients at higher risk, such as those with diabetes, higher levels of blood pressure, and the metabolic syndrome. These patients need multiple medications for treatment of concurrent risk factors and conditions (Wald and Law 2003; Sleight et al 2006). Furthermore, combination therapy may be cost effective because of the potential for reduced drug costs (eg, fewer co-payments), better blood pressure control, improved compliance, and fewer discontinuations and switches between therapies (Ambrosioni 2001).

We believe that ARB/HCTZ combinations, such as losartan/HCTZ, may be superior to ACEI/HCTZ and other antihypertensive agent/HCTZ combinations because of 1) the better tolerability of ARBs and 2) available outcomes data. Although ramipril compared with placebo therapy significantly lowered the risk for stroke in patients with his-

tory of cardiovascular disease with or without hypertension in the HOPE study (The Heart Outcomes Prevention Evaluation Study Investigators 2000), these results that may have been influenced by blood pressure differences between the groups favoring ramipril as shown in an ambulatory blood pressure substudy (Svensson et al 2001). Data from clinical trials with ACEIs suggest a neutral effect on outcomes compared with traditional antihypertensive treatment for the same degree of blood-pressure lowering in patients with hypertension and high risk for cardiovascular disease (Kjeldsen et al 2005b; Williams 2005). Interestingly, in the perindopril protection against recurrent stroke study (PROGRESS), which compared single therapy with perindopril versus placebo or dual therapy with perindopril plus indapamide versus placebo in patients with a history of cerebrovascular disease, only combination treatment, not the ACEI alone, significantly reduced stroke incidence (PROGRESS Collaborative Group 2001). Data from clinical trials suggest that ARBs have benefits on non-coronary outcomes compared with traditional treatment; however, there have been some inconsistencies in the results of ARB trials due to problems with equalizing blood pressures in the treatment groups (Kjeldsen et al 2005b). Treatment with losartan in the LIFE study was associated with a significant risk reduction for stroke in the context of blood pressure reductions similar to those achieved in the active comparator (atenolol) group. Similar results were observed for stroke or transient ischemic attack in the Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention (MOSES) study of eprosartan-based or nitrendipine-based therapy (Schrader et al 2005). It remains to be seen whether comparable advantages will be seen with other ARBs compared with other classes of antihypertensive drugs in long-term outcome studies.

Stroke is a devastating outcome in patients with hypertension. The efficacy, tolerability, and convenience of losartan/HCTZ combination therapy may increase patient compliance and reduce risk for stroke.

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