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 (AT1) 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
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 antithrombotic 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.
Losartan/HCTZ to reduce stroke risk

Losartan/HCTZ to reduce stroke risk (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 (Dahlof et al 2002). Several potential mechanisms that may be responsible for the beneficial effect of losartan in the LIFE study have been suggested (Dahlof et al 2002; Mancia 2004; Devereux and Dahlof 2007a): attenuation of arterial stiffness; inhibition of angiotensin II-induced endothelial dysfunction (Schiffrin et al 2000); inhibition of hypertension, 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.

Table 1 Stroke subtypes by treatment in the LIFE study

| Stroke type            | Losartan (n = 4605) | Atenolol (n = 4588) | Adjusted* hazard ratio (95% CI) | p-value | Unadjusted hazard ratio (95% CI) | p-value |
|------------------------|---------------------|---------------------|---------------------------------|---------|---------------------------------|---------|
| 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   |

*For degree of left ventricular hypertrophy and Framingham risk score at randomization.

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**Abbreviations**: CI, confidence interval.
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).

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

...hypertensive 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).

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 (Hoeiegen 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 ramiplril 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.

References
The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. 2002. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA, 288:2981–97.

Ambrosioni E. 2001. Pharmacoeconomics of hypertension management: the place of combination therapy. Pharmacoeconomics, 19:337–47.

Amer J. 2002. Hypertension in high-risk patients: beware of the undertuse of effective combination therapy (results of the PRATIK study). J Hypertens, 20:779–84.

Anderson A, Morgan TO. 1990. Interaction of enalapril with sodium restriction, diuretics, and slow-channel calcium-blocking drugs. Nephron, 55 (Suppl 1):70–2.

Brunner HR, Gavras H, Waecher B. 1980. Enhancement of diuretics of the antihypertensive action of long-term angiotensin converting enzyme blockade. Clin Exp Hypertens, 2:639–57.

Chapman RH, Benner JS, Petrella AA, et al. 2005. Predictors of adherence with antihypertensive and lipid-lowering therapy. Arch Intern Med, 165:1147–52.

Chobanian AV, Bakris GL, Black HR, et al. 2003. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report. JAMA, 289:2560–71.

Conlin PR, Spence JD, Williams B, et al. 2000. Angiotensin II antagonists for hypertension: are there differences in efficacy? Am J Hypertens, 13:418–26.

Dahlof B, Devereux R, de Faire U, et al. 1997. The Losartan Intervention For Endpoint Reduction (LIFE) in Hypertension Study. Rationale, design, and methods. Am J Hypertens, 10:705–13.

Dahlof B, Devereux RB, Julius S, et al. 1998. Characteristics of 9194 patients with left ventricular hypertrophy: The LIFE Study. Hypertension, 32:989–97.

Dahlöf B, Devereux RB, Kjeldsen SE, et al. 2002. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet, 359:995–1003.

Dahlof B, Devereux RB, Kjeldsen SE. 2004. Diuretics in the LIFE study. Lancet, 364:413–4.

Devereux RB, Dahlöf B, Gerds E, et al. 2004. Regression of hypertensive left ventricular hypertrophy by losartan compared with atenolol: The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Trial. Circulation, 110:1456–62.

Devereux RB, de Faire U, Fyhquist F, et al. 2007. Blood pressure reduction and antihypertensive medication use in the losartan intervention for endpoint reduction in hypertension (LIFE) study in patients with hypertension and left ventricular hypertrophy. Curr Med Res Opin, 23:259–70.

Devereux RB, Dahlöf B. 2007. Potential mechanisms of stroke benefit favoring losartan in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study: data from a multicenter, randomized, double-blind, 12-week trial. Clin Ther, 23:1166–79.

Fields LE, Burt VL, Cutler JA, et al. 2004. The burden of adult hypertension in the United States 1999 to 2000: A rising tide. Hypertension, 44:398–404.

Gleim GW, Rubino J, Zhang H, et al. 2006. A randomized, double-blind trial of the antihypertensive efficacy and tolerability of once-daily losartan 100 mg/hydrochlorothiazide 12.5 mg combination compared with losartan 100 mg monotherapy in the treatment of mild-to-severe essential hypertension. Clin Ther, 28:1639–48.

Goldstein LB, Adams R, Alberts MJ, et al. 2006. Primary prevention of ischemic stroke: a guideline from the American Heart Association/ American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Stroke, 37:1583–633.

Gradman AH, Brady WE, Gazdick LP, et al. 2002. A multicenter, randomized, double-blind, placebo-controlled, 8-week trial of the efficacy and tolerability of once-daily losartan 100 mg/hydrochlorothiazide 25 mg and losartan 50 mg/hydrochlorothiazide 12.5 mg in the treatment of moderate-to-severe essential hypertension. Clin Ther, 24:1049–61.

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Guidelines Committee. 2003. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens, 6:1011–53.

Hajjar I, Kotchen TA. 2003. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988–2000. JAMA, 290:199–206.

Hall WD. 1998. Pharmacologic therapy of hypertension in blacks. J Clin Hypertens, 3(Suppl 3):108S–113S.

Hansson L, Lindholm LH, Niskanen L, et al. 1999. Effect of angiotensin-converting-enzyme inhibitor compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. Lancet, 353:611–6.

The Heart Outcomes Prevention Evaluation Study Investigators. 2000. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med, 342:145–53.

Hoieggen A, Alderman MH, Kjeldsen SE, et al. 2004. The impact of serum uric acid on cardiovascular outcomes in the LIFE study. Kidney Int, 65:1041–9.

Ibsen H, Wachtell K, Olsen MH, et al. 2004. Does albuminuria predict cardiovascular outcome on treatment with losartan versus atenolol in hypertension with left ventricular hypertrophy? A LIFE substudy. J Hypertens, 22:1805–11.

Julius S, Alderman MH, Bevers G, et al. 2004a. Cardiovascular risk reduction in hypertensive black patients with left ventricular hypertrophy. The LIFE study. J Am Coll Cardiol, 43:1047–55.

Julius S, Kjeldsen SE, Weber M, et al. 2004b. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet, 363:2022–31.

Kizer JR, Hoieggen A, Alderman MH, et al. 2004. Serum uric acid and ischemic stroke risk among hypertensive patients with left ventricular hypertrophy: The losartan intervention for endpoint reduction in hypertension (LIFE) study. J Am Coll Cardiol, 43 (5, suppl A):475A.

Kizer JR, Dahlof B, Kjeldsen SE, et al. 2005. Stroke reduction in hypertensive adults with cardiac hypertrophy randomized to losartan versus atenolol: the Losartan Intervention For Endpoint reduction in hypertension study. Hypertension, 45:46–52.

Kizer JR, Devereux RB. 2006. Regression of left ventricular hypertrophy: lodestar to stroke prevention in the treatment of hypertension? Am J Hypertens, 19:439–444.

Kjeldsen SE, Julius S, Hedner T, et al. 2001. Stroke is more common than myocardial infarction in hypertension: analysis based on 11 major randomized intervention trials. Blood Press, 10:190–2.

Kjeldsen SE, Os I, Hoieggen A, et al. 2005a. Fixed-dose combinations in the management of hypertension: defining the place of angiotensin receptor antagonists and hydrochlorothiazide. Am J Cardiovasc Drugs, 5:17–22.

Kjeldsen SE, Lyle PA, Tershakovec AM, et al. 2005b. Targeting the renin-angiotensin system for the reduction of cardiovascular outcomes in hypertension: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Expert Opin Emerg Drugs, 10:729–45.

Lindholm LH, Ibsen H, Borch-Johnsen K, et al. 2002. Risk of new-onset diabetes in the Losartan Intervention For Endpoint Reduction in hypertension study. J Hypertens, 20:1879–86.

Lindholm LH, Persson M, Alaupovic P, et al. 2003. Metabolic outcome during 1 year in newly detected hypertensives: results of the Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation (ALPINE) study. J Hypertens, 21:1563–74.

Lithell H, Hansson L, Skog O, et al. 2003. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. J Hypertens, 21:875–86.

MacGregor GA, Markandu ND, Singer DR, et al. 1987. Moderate sodium restriction with angiotensin converting enzyme inhibitor in essential hypertension: a double blind study. BMJ, 294:531–4.

Mancia G. 2004. Prevention and treatment of stroke in patients with hypertension. Clin Ther, 26:631–48.

Mulrow C, Lau J, Cornell J, et al. 2000. Pharmacotherapy for hypertension in the elderly. Cochrane Database Syst Rev, CD000028.

Navis G, de Jong PE, Donker A, et al. 1987. Moderate sodium restriction in hypertensive subjects: renal effects of ACE-inhibition. Kidney Int, 31:815–9.

Okin PM, Devereux RB, Jern S, et al. 2003. Regression of electrocardiographic left ventricular hypertrophy by losartan versus atenolol: The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study. Circulation, 108:684–90.

PROGRESS Collaborative Group. 2001. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. Lancet, 358:1033–41.

Patsy BM, Lumley T, Furbeger CD, et al. 2003. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. JAMA, 289:2534–44.

Rosamond W, Flegal K, Friday G, et al. 2007. Heart disease and stroke statistics—2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 115:e69–171.

Sadoshima J. 2002. Novel AT(1)-receptor-independent functions of losartan. Circ Res, 90:754–6.

Salerno CM, Demopoulous L, Mukherjee R, et al. 2004. Combination angiotensin receptor blocker/hydrochlorothiazide as initial therapy in the treatment of patients with severe hypertension. J Clin Hypertens (Greenwich), 6:614–20.

Sassano P, Chatellier G, Billard E, et al. 1989. Comparison of increase in the enalapril dose and addition of hydrochlorothiazide as second-step treatment of hypertensive patients not controlled by enalapril alone. J Cardiovasc Pharmacol, 13:314–9.

Schiffrin EL, Park JB, Intengan HD, et al. 2000. Correction of arterial structure and endothelial dysfunction in human essential hypertension by the angiotensin receptor antagonist losartan. Circulation, 101:1653–9.

Schrader J, Luders S, Kulschewski A, et al. 2005. Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention: principal results of a prospective randomized controlled study (MOSES). Stroke, 36:1218–26.

Singer DR, Markandu ND, Cappuccio FP, et al. 1995. Reduction of salt intake during converting enzyme inhibitor treatment compared with addition of a thiazide. Hypertension, 25:1042–4.

Sleight P, Pouleur H, Zannad F. 2006. Benefits, challenges, and registerability of the polypill. Eur Heart J, 27:1651–6.

Stier CT, Adler LA, Levine S, et al. 1993. Stroke prevention by losartan in stroke-prone spontaneously hypertensive rats. J Hypertens, 11:S37–42.

Straus SE, Majumdar SR, McAlister FA. 2002. New evidence for stroke prevention: scientific review. JAMA, 288:1388–95.

Svensson P, de Faire U, Sleight P, Yusuf S, Ostergren J. 2001. Comparative effects of ramipril on ambulatory and office blood pressure: a HOPE substudy. Hypertension, 38:E28–32.

Wachtell K, Hornestam B, Leho M, et al. 2005. Cardiovascular morbidity and mortality in hypertensive patients with a history of atrial fibrillation: The Losartan Intervention for End Point Reduction in Hypertension (LIFE) Study. J Am Coll Cardiol, 45:705–11.

Waebner B. 2003. Combination therapy with ACE inhibitors/angiotensin II receptor antagonists and diuretics in hypertension. Expert Rev Cardiovasc Ther, 1:43–50.

Wald NJ, Law MR. 2003. A strategy to reduce cardiovascular disease by more than 80%. BMJ, 326:1419. Erratum in BMJ, 2003. 327:586 and BMJ, 2006. 360:823.

Warlow CP. 1998. Epidemiology of stroke. Lancet, 352:S1–4.

Weinberger MH. 1985. Blood pressure and metabolic responses to hydrochlorothiazide, captopril, and the combination in black and white stroke-prone spontaneously hypertensive rats. Hypertension, 10:729–45.
Wolf PA, D’Agostino RB, O’Neal A, et al. 1992. Secular trends in stroke incidence and mortality. The Framingham Study. *Stroke*, 23:1551–5.
Wolf-Maier K, Cooper RS, Banegas JR, et al. 2003. Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. *JAMA*, 289:2363–9.
Wolz M, Cutler J, Roccella EJ, et al. 2000. Statement from the National High Blood Pressure Education Program: prevalence of hypertension. *Am J Hypertens*, 13:103–4.
Wright JT Jr. 1988. Profile of systemic hypertension in black patients. *Am J Cardiol*, 61:41H–45H.
