Role of antihypertensive therapy with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers in combination with calcium channel blockers for stroke prevention

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Abstract

Objective: To review the available literature on the effects of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and calcium channel blockers (CCBs) or combinations of these agents on stroke outcomes in hypertensive patients.

Data sources: A Medline search was conducted using the search terms *stroke* and *antihypertensives*, *calcium channel blockers*, *angiotensin-converting enzyme inhibitors*, or *angiotensin II receptor blockers* from 1985 to August 17, 2009.

Study selection: Randomized controlled clinical trials with at least 400 randomized patients were selected if at least one of the treatment arms used a CCB, ACEI, or ARB to evaluate stroke outcomes in hypertensive patients.

Data synthesis: The prevalence of stroke is high in the United States, accounting for approximately 150,000 deaths per year. Early identification and treatment of hypertension to quickly achieve blood pressure reduction is critical in the prevention of stroke. Many trials have provided evidence that CCBs, ACEIs, and ARBs are effective in stroke prevention. Most patients require two or more antihypertensive drugs to achieve blood pressure goals. Because of their complementary actions, combination antihypertensive therapy with a renin–angiotensin–aldosterone system (RAAS) blocker and a CCB may help reduce stroke incidence to a greater extent than either of the monotherapies.

Conclusion: A growing body of clinical trial data suggest that aggressive combination antihypertensive therapy, including a RAAS blocker and CCB, may help reduce stroke incidence. Fixed-dose combination therapy is an important consideration in optimizing blood pressure control and patient adherence to therapy in stroke prevention.

Keywords: Hypertension, antihypertensive agents, stroke prevention and treatment, pharmacotherapy, blood pressure.

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The prevalence of stroke is high in the United States and carries a tremendous burden that can include disability or death. Annual rates for new and recurrent stroke among adults 20 years or older are estimated at approximately 610,000 and 185,000, respectively,[1,2] with the prevalence of stroke being approximately 6.5 million in 2006.[2] For 2008, total direct and indirect costs of cardiovascular diseases and stroke in the United States were estimated at $448.5 billion.[3] For stroke alone, lost productivity resulting from morbidity and mortality totaled $21.8 billion, with direct costs (hospitalization and nursing home services, physicians and other professionals, and medical durables and home health care) accounting for an additional $43.7 billion.[3] Stroke accounted for approximately 1 of every 16 deaths in the United States in 2004 (150,000 deaths/year)[4] and, when considered separately from other cardiovascular diseases, ranked third among all causes of death following heart disease and cancer.[3] Despite these sobering statistics, evidence of progress also exists. From 1994 to 2004, the stroke death rate decreased 24.2% and the actual number of stroke deaths declined by 6.8%.[3] However, there is considerable room for improvement.

In general, stroke incidence rates are greater for men than for women, but this difference disappears with age.[3] Stroke incidence varies greatly according to geographic location and ethnicity.[3] For example, the overall prevalence of stroke across the United States has decreased from 1994 to 2004 in every state by 5.7% (Alabama) to 34.5% (Minnesota).[3] The southeastern region of the United States is often referred to as the "stroke belt" because of the high rates of stroke mortality in the region. However, five states elsewhere in the country (Illinois, Michigan, Missouri, Nevada, Texas, and West Virginia) also have prevalence estimates of 3.0% or higher.[3] Recent estimates (2005) for ethnicity showed that blacks were twice as likely to incur a first-ever stroke compared with whites.[3] At ages 45 to 84 years, the age-adjusted stroke incidence for black men and women is 6.6 and 4.9 per 1,000 population, respectively. The prevalence of stroke among blacks was 3.4% compared with 2.3% for whites and 2.0% for Asians.[3] In a 20-year follow-on study initiated in 1965 comparing risk of hospitalized stroke in American men from the Framingham study with Japanese American men in the Honolulu Heart Study, it was demonstrated (after adjusting for age and other risk factors) that Framingham men (62 of 1,000) had a 40% excess of thrombotic stroke compared with Japanese American men (45 of 1,000, $P < 0.001$).[5] Among American Indians 65 to 74 years of age, new and recurrent strokes occur at a similar frequency for men and women (6.1 vs. 6.6 per 1,000).[3] According to the BASIC (Brain Attack Surveillance in Corpus Christi) project, Mexican Americans (16.8 of 1,000) have an increased incidence of stroke compared with non-Hispanic whites (13.6 of 1,000).[3]

Stroke can be categorized into two broad types: ischemic stroke, which accounts for approximately 88% of all stroke, and hemorrhagic stroke, which accounts for 12% of all stroke[4,6]; each of these types of stroke can be subcategorized by mechanism, which, in the case of ischemic stroke, may include atherosclerotic cerebrovascular disease, penetrating artery disease (lacunes), and cardiogenic embolism (Figure 1).[7,8]

Clinical management of stroke is guided by evaluation of patient risk factors. Risk factors for stroke are categorized as (1) nonmodifiable risk factors, including factors such as age, gender, or race; (2) modifiable risk factors, the improvement of which has documented benefit in reducing cerebrovascular risk such as hypertension, cardiac disease, diabetes, or obesity; and (3) potentially modifiable but less well-documented risk factors, including oral contraceptive use, migraine, and sleep-disordered breathing.[8,9]

Recent estimates (2005) suggested that more than 70 million Americans (1 in 3 adults) have the modifiable risk factor hypertension[1,3,10]—up from 43.1 million in 1991.[11] Hypertension correlates with an increase in cardiovascular events,[12] including stroke, for which it is the greatest risk factor.[3] For every 20–mm Hg increase in systolic blood pressure (SBP) or 10–mm Hg increase in diastolic blood pressure (DBP), stroke mortality doubles (Figure 2).[13,14] In one analysis of data from the Framingham Heart Study, it was estimated that an average reduction in DBP by 2 mm Hg among white men aged 35 to 64 years would reduce risk of stroke by 14%, prevalence of hypertension (DBP ≥90 mm Hg) by 17%, and risk of coronary artery disease by 6%.[15] For those 49 to 69 years, each 20–mm Hg reduction in usual SBP is associated with a twofold reduction in stroke mortality without any evidence of a plateau at least to 115/75 mm

At a Glance

Synopsis: Hypertension is a major risk factor for stroke that often requires treatment with two or more drugs to reach goal blood pressure in most patients. The literature was reviewed to determine the effects of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and calcium channel blockers (CCBs) or combinations of these agents on stroke outcomes in hypertensive patients. Identifying hypertension quickly and aggressively lowering blood pressure to goal with combination therapy, including a renin–angiotensin–aldosterone system (RAAS) blocker and CCB, may be critical to reducing stroke incidence.

Analysis: *Estimates from 2005 showed that blacks were twice as likely to experience a first-ever stroke compared with whites. Evidence from ALLHAT suggests that a diuretic should be part of the antihypertensive regimen in black patients. Activation of RAAS is a major contributor to hypertension development in about two-thirds of patients; therefore, suppression of RAAS is a rational initial target for blood pressure control. Fixed-dose combination therapy may improve patient adherence to therapy compared with multiple-drug combination therapy, but potential disadvantages of fixed-dose combination therapy include low numbers of combination products, most of which are branded and therefore more expensive, and limited ability to titrate individual component doses.*