

# Hypertension in women

Suzanne Oparil, M.D.

*Vascular Biology and Hypertensive Program, Division Cardiovascular Disease, University of Alabama at Birmingham, 35294, USA*

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in American women and claims the lives of more than half a million women every year. Elevated blood pressure (BP) is the most common modifiable risk factor for CVD, including stroke, myocardial infarction (MI) and renal failure. MI is the leading cause of death, and stroke, the third most common cause of death and the leading cause of disability among American women. Coronary heart disease (CHD) rates in postmenopausal women are 2-3 times those of premenopausal women. Mortality from CVD is increasing in women after decades of trending downward, whereas in men the downward trend is continuing. Prevention of CVD events through the appropriate management of hypertension is an important public health issue for postmenopausal women, particularly as the female population in the US is aging.

Clinical trials have shown the benefit of pharmacologic treatment of hypertension in the elderly (both men and women) in reducing CVD morbidity and mortality. Most large multi-center trials of antihypertensive therapy with "hard" endpoints in this group have included a large proportion of women. Two milestone placebo controlled trials in elderly patients with ISH, the Systolic Hypertension in the Elderly (SHEP) trial and the Systolic Hypertension in Europe (Syst-Eur) trial, showed highly significant reductions in stroke and CVD events. These effects were observed with treatment regimens that began with a diuretic or a dihydropyridine calcium channel blocker (CCB) and added other drugs as needed to achieve goal BP. A meta analysis that included these and other placebo controlled trials of treatment of ISH in the elderly showed significant reductions in stroke (30%), total mortality (13%), CVD mortality (18%), all CVD complications (26%) and coronary events (23%) (16). These trials used a variety of active agents, including diuretics, beta-blockers (BB), reserpine, CCBs, angiotensin converting enzyme inhibitors (ACEIs) and  $\alpha$ -methyldopa.

More recent studies have compared the efforts of active treatment regimens on CVD morbidity and mortality in high-risk, generally elderly hypertensive patients.

Comparisons between ACEIs, CCBs, BBs, and diuretics or combinations of these agents have demonstrated no major differences between treatment groups in CVD outcomes. ACEI-based regimens appeared to be somewhat more effective than CCB-based regimens in preventing coronary events and CHF; CCB-based regimens were slightly more effective than ACEI-based regimens in preventing stroke but these small differences could be attributed to chance. The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial has provided the first evidence that a newer antihypertensive agent, the angiotensin II receptor blocker (ARB) losartan, has benefits beyond established antihypertensive therapy with a BB in high-risk hypertensive patients. LIFE showed 25% reductions in stroke and new onset diabetes with ARB compared to BB treatment. Further, a 40% reduction in all cause mortality was seen in diabetics treated with losartan, and losartan was much better tolerated than the BB. BP was lowered to a similar extent with both treatments. Women responded even better than men to antihypertensive treatment based on losartan.

A subgroup meta analysis of individual patient data according to sex based on 7 trials from the Individual Data Analysis (INDANA) of antihypertensive intervention trials database showed comparable reductions in stroke and major cardiovascular events in both sexes in response to diuretic and/or BB treatment. Women had a somewhat lower absolute risk reduction for coronary events than did men, but the analysis showed a trend toward benefit with active treatment in women, as well.

Based on this evidence, elderly patients, including postmenopausal women, clearly benefit from antihypertensive treatment through reduction of cardiovascular morbidity and mortality rates. Older conventional antihypertensive drugs (diuretics and BBs) and the newer drugs (ACEIs, CCBs) appear to be equally useful in reducing CVD outcomes in elderly patients with combined systolic and diastolic hypertension. In patients with ISH, evidence for benefit is greatest with diuretics and CCBs, and these agents are designated as

"preferred" by JNC-VI. The recent report of dramatic superiority of ARB-based treatment compared to BB-based treatment in elderly patients with either systolic and diastolic hypertension or ISH with LVH raises the possibility that this new antihypertensive drug class may be more effective than others in preventing CVD outcomes. Further clinical trial data are needed to resolve this issue. Elderly hypertensive patients have a high prevalence of comorbid conditions and target organ damage which dictate the choice of antihypertensive drugs. For example, ACEIs are indicated in patients with atherosclerosis, post MI, CHF, renal insufficiency, and type I diabetes with proteinuria. ARBs are indicated for these conditions in ACE intolerant patients and may be the drug of choice in type 2 diabetes with proteinuria. Whether ARBs are equivalent to ACEIs is currently under study. BBs are indicated for patients with angina and post-MI. Diuretics are especially useful in women because they help to prevent osteoporosis and reduce the risk of hip fracture.

Management is also guided by the adverse effect profile of a particular agent, which may be gender specific. Women are more likely to develop hyponatremia

and hypokalemia with thiazide diuretics, while men are more likely to develop gout. ACEI induced cough is twice as common in women than in men and pedal edema with a CCB is more common in women. Importantly, this represents a guide to specific drug classes that should be included in the antihypertensive regimen and not a mandate for a particular choice of monotherapy. Most patients require multiple agents to achieve aggressive BP goals, and it is likely that getting BP to goal is more important than choice of individual antihypertensive drugs.

In conclusion, postmenopausal HTN is highly prevalent in the population and is a significant cause of morbidity and mortality in elderly women. Early recognition and management of this modifiable condition can help to prevent or reduce the occurrence of CVD, including MI, stroke, CHF, and end-stage renal disease. Lifestyle modification and pharmacological treatment of hypertension are particularly effective in the elderly, and achievement of aggressive BP goals, usually with multiple antihypertensive drugs, will result in improved quality of life and increased longevity in postmenopausal women.