

## Therapeutic Advances: Hypertension in the Elderly

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The incidence of hypertension and attendant biological disorders (loss of arterial wall elasticity, endothelial dysfunction, insulin resistance) increases with age and so does the frequency of cardiovascular complications. Women have a lower incidence of hypertension and a later—by an average of 10 years—onset of cardiovascular complications. During the premenopausal years, women seem to be relatively protected from cardiovascular events, in part through the effects of estrogen on endothelial function and lipid profile. After menopause however, the incidence of cardiovascular events tends to become similar in both genders, and the severity of such events, in terms of morbidity and mortality, is actually higher in women. The role of hormone replacement for cardiovascular protection has been shown to offer no long-term benefits: indeed, despite improvement in surrogate endpoints (endothelial function, lipid profile), in long-term prospective randomized trials there was no advantage in outcomes, possibly because benefits are offset by the thrombogenic and carcinogenic properties of estrogen.

Over age 65 the prevalence of hypertension can reach more than 50%. Systolic hypertension predominates, but is itself an important risk factor and marker of cardiovascular complications. Special considerations affecting choice of antihypertensive agents for elderly patients include knowledge of the normal pathophysiologic alterations of aging, assessment of coexisting diseases or target organ complications, consideration of the pharmacodynamics and kinetics of each class of antihypertensive agents and potential drug interactions when treating the frequently coexisting diseases, such as diabetes mellitus, chronic obstructive pulmonary disease, arthritis, etc.

Contrary to previous assumptions, elderly hypertensives are not resistant to newer antihypertensive agents such as angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II type 1 receptor blockers (ARBs), and in fact appear to respond to lower doses with incidence of side-effects generally similar to that of younger individuals. ACEIs, ARBs and calcium channel blockers seem to have several advantages in comparison to older antihypertensive agents in this population, mostly because of lack of metabolic disturbances and of central nervous system-mediated side-effects (drowsiness, forgetfulness, fatigue etc) that adversely affect the quality of life of these patients. The newest antihypertensive drug class, direct renin inhibitors (DRI), whose first member, aliskiren, has recently become available, has not yet been studied specifically in elderly hypertensives. However, in view of its mechanism of action, it would be expected to have a pharmacologic profile essentially similar to that of ACEIs and ARBs.

Evidence of the value of pharmacologic therapy in elderly patients with isolated systolic hypertension (ISH) was first provided in 1992 by the Systolic Hypertension in the Elderly Program (SHEP). However, as the BP treatment in those years was based mostly on thiazide diuretics, the benefits of BP lowering came at the price of significant adverse metabolic effects, including hypokalemic, hyperuricemia and increased rate of

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new-onset type 2 diabetes mellitus, which required additional therapeutic interventions.

The question of whether patients over age 80 may benefit from antihypertensive treatment was recently answered by the Hypertension in the Very Elderly Trial (HYVET), published in 2008. Treatment with indapamide, in most cases in combination with perindopril, showed within 2 years reductions in the rate of stroke and heart failure by 30% and 64%, respectively and reduction in death from any cause by 21%. These data demonstrate that benefits of antihypertensive therapy outweigh the risks even in patients of advanced age.

In conclusion, it is now well established that pharmacologic interventions to lower elevated blood pressure are safe and effective in all ages, even for patients with multiple comorbidities. Concern about adverse drug interactions has been an important limitation in the past, but has been alleviated with the advent of newer, safer classes of antihypertensive agents. The wide array of novel available drugs permits selection of agents that will not interfere with the pathophysiology or pharmacotherapy of commonly coexisting conditions, such as diabetes, chronic obstructive pulmonary disease or musculoskeletal disorders.