

# Reevaluating the Use of Antihypertensive Medications, a First Step Toward Reducing Polypharmacy in Very Old Patients

Vito M. Campese, MD;<sup>1</sup> Edward L. Schneider, MD<sup>2,3,4</sup>

In this Commentary, we propose the reevaluation of the usage of antihypertensive medications in very old patients. We further recommend the initiation of clinical trials to determine if taking selected patients with orthostatic hypotension (OH) off their antihypertensive medications may reduce their morbidity and mortality.

## THE CHALLENGE: POLYPHARMACY IN AGED PATIENTS

The oldest old are the fastest growing age group in the United States. In 1900, only 6053 out of 100,000 (6%) at birth would be expected to reach age 85. By 2004, 38% were expected to reach age 85, a 6-fold increase.<sup>1</sup> Future estimates of population growth indicate that the growth of this group will further increase by 3-fold from 1.5% of the total US population to 4.3% in 2050 with the advent of aged baby boomers.<sup>2</sup>

*From the Keck School of Medicine;<sup>1</sup> the Leonard Davis School of Gerontology;<sup>2</sup> the Division of Geriatric, Hospital and General Internal Medicine, Keck School of Medicine;<sup>3</sup> and the College of Letters, Arts and Sciences, University of Southern California, Los Angeles, CA<sup>4</sup>*

*Address for correspondence:*

*Vito M. Campese, MD, Keck School of Medicine, USC, 2020 Zonal Avenue, Los Angeles, CA 90033  
E-mail: campese@usc.edu*

Past age 50, the number of medications prescribed to older Americans rises with each decade as the number of chronic conditions increases. In 2003, cardiovascular agents accounted for a quarter (25.2%) of prescription drug spending by Medicare beneficiaries ages 65 and older. In a study of community dwelling older Americans, 6 of the 13 most frequently prescribed medications were used for the control of elevated blood pressure (BP).<sup>3</sup> Therefore, antihypertensive medications may be a good starting point for reevaluating medication usage by very old Americans.

## HYPERTENSION-RELATED MORBIDITY AND MORTALITY

Among persons 80 years or older, nearly 75% have been diagnosed with hypertension, and more than 60% have stage 2 hypertension and/or are receiving treatment. Remarkably, only 7% of the oldest group ( $\geq 80$  years of age) had normal BP. It is expected that the reduction of BP in patients with elevated systolic BP (SBP) or diastolic BP (DBP) will reduce the risk of heart disease and stroke and increase life expectancy. This expectation is supported by several clinical trials (11 for stroke alone). A recent randomized placebo controlled trial (Hypertension in the Very Elderly Trial [HYVET]) included 3854 patients ages 80 and older who received a combination of indapamide and perindopril. The study reported a 30% reduction in the risk of stroke (the primary endpoint of the study), 23% reduction in the rate of death from cardiovascular disease, and a 21% reduction in the

doi: 10.1111/j.1751-7176.2010.00304.x



rate of death from all causes.<sup>4</sup> These results may lead to increased use of antihypertensive drugs in the elderly regardless of age and comorbidities. However, this study has serious limitations. One limitation is that patients in HYVET are not representative of the majority of elderly patients with hypertension. 95% of patients who were enrolled in the trial (3670 of 3845) came from Eastern Europe and China. Since Eastern Europeans have an increased rate of death from stroke,<sup>5</sup> one has to wonder whether the beneficial effects of antihypertensive therapy in these high-risk, stroke-prone populations apply in lower-risk American populations. HYVET did not report the number of patients screened vs those enrolled. Of every 100 patients who were contacted in the Systolic Hypertension in the Elderly Program (SHEP) trial,<sup>6</sup> only 12 met the initial study criteria, 3 completed a baseline visit, and only 1 underwent randomization. Therefore, the findings of the SHEP and HYVET studies may not necessarily be applicable to all elderly hypertensive patients. Finally, these studies did not address the issue of treatment of hypertension in patients with concomitant OH.

#### **RATIONALE FOR TAKING SELECTED PATIENTS OFF ANTIHYPERTENSIVE MEDICATIONS**

Our review of the literature on antihypertensive medications suggests that many patients benefit from antihypertensive medications. However, many very old patients have been on these medications for several decades with no attempt to find out if they still need them. Furthermore, most antihypertensive medications have common side effects. For example, diuretics, which are usually the first medications utilized for the treatment of hypertension in the elderly, can cause dehydration, gout, hyponatremia, and nocturia. Among the side effects of  $\beta$ -blockers are insomnia, tiredness, depression, and impotency. Angiotensin-converting enzyme inhibitors can cause coughing and skin rashes. Angiotensin II receptor blockers can cause dizziness. Calcium channel blockers may cause palpitations, constipation, headache, dizziness, and peripheral edema. All these medications can cause or aggravate OH. Many elderly individuals are on 3 or 4 of these medications. Obviously, weaning patients from antihypertensive agents may reduce their risk of these side effects. Furthermore, a recent study has shown that overly aggressive treatment of hypertension with a combination of ramipril and telmisartan, rather than with any single drug given alone, may increase the probability of developing

endstage kidney failure in adults and older persons (the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial [ONTARGET]).<sup>7</sup>

In a Japanese study of the association between SBP and mortality in 80-year-old patients, there appeared to be no relation between the risk of mortality and the level of BP.<sup>8</sup> In population based Established Populations for Epidemiologic Studies of the Elderly (EPESE) studies conducted in Boston, New Haven, Iowa, and North Carolina, in men age 85 and older, higher SBP was associated with increased survival.<sup>9</sup> In a longitudinal study of 795 men and women at Rancho Bernardo, California, a drop in BP of 5 mm Hg was associated with poor survival in men after age 75. The risk was strongest in men who took antihypertensive medications.<sup>10</sup> Using a logistic splines to model the relation of risk of cardiovascular and all-cause death with SBP and age, Port and colleagues<sup>11</sup> found that, against the predictions of the linear logistic model, neither all-cause nor cardiovascular deaths depended on SBP in a strictly increasing manner.

In a prospective, population-based cohort study of 3078 men and women, initial age 55 to 84 from the Rotterdam Study and 276 men and women, initial age 85, from the Leiden 85+ Study, Euser and colleagues observed that in the youngest participants (<65), SBP and DBP were not associated with cognitive function 11 years later. For persons aged 65 to 74, higher baseline SBP and DBP were related to worse cognitive function 11 years later. In contrast, in older age (>75), higher SBP and DBP seemed to be related to better cognitive function at the end of follow-up. This effect appeared strongest in the highest age group (aged 85).<sup>12</sup> These studies suggest that there may actually be a benefit in terms of mortality and morbidity with the weaning of antihypertensive medications in some very old patients.

#### **SELECTED GROUP: ELDERLY PATIENTS WITH OH**

While older Americans have a very high prevalence of hypertension, many of these patients also have OH. OH is defined by the Consensus Committee of the American Autonomic Society and the American Academy of Neurology as a decline of >20 mm Hg in SBP or a decline of >10 mm Hg in DBP that occurs when a person moves from a supine to a sitting or standing position. The decrease must be present within 3 minutes after the postural change. The prevalence of OH varies in different populations and increases with age. In the

Cardiovascular Health Study, the prevalence of OH was 14.8% for persons aged 65 to 69 and 26% for those aged 85 and older.<sup>13</sup> In another study, OH occurred in 14.6% of community dwelling older adults and in 52% of nursing home residents.<sup>14</sup> In a study of home-dwelling, elderly aged 75 years or older population, the prevalence of OH was 34%.<sup>15</sup>

The mechanisms responsible for OH among older patients are complex and may include volume depletion, deconditioning, autonomic dysfunction, arterial stiffness, cardiac diseases, central nervous system disorders, dementia, venous diseases, amyloidosis, and antihypertensive medications.  $\beta$ -blockers appear to be more likely to cause OH than other antihypertensive drugs. Psychotropic drugs, which are commonly used in older patients, may further augment this problem.

In elderly individuals, OH is a frequent cause of falls, which may result in serious complications, such as fractures and head injuries. OH can result in syncope, brain hypoperfusion with cognitive decline, fear of falling, impaired quality of life, and increased risk of stroke. In a cohort of 3522 Japanese-American men 71 to 93 years old, the 4-year, age-adjusted mortality rates in those with and without OH were 56.6 and 38.6 per 1000 person-years, respectively. There was a significant linear association between change in SBP from supine position to standing and 4-year mortality rates ( $P < .001$ ) suggesting a dose-response relation.<sup>16</sup>

OH is very prevalent among elderly patients, particularly in nursing home residents and those with comorbidities. Despite the high prevalence of OH in the elderly, BP is not usually tested in the upright position either in physician offices or in nursing homes. We suggest that weaning very old patients (older than 80) with OH off their antihypertensive medications may reduce the risks and complications of OH.

#### CONTRAINDICATIONS TO TAKING PATIENTS OFF THEIR ANTIHYPERTENSIVE MEDICATIONS

There are many obvious contraindications for taking older patients off antihypertensive medications. These include: patients with resistant hypertension; those with estimated glomerular filtration rate  $< 30$  mL/min per  $1.73$  m<sup>2</sup>; patients with clinical evidence of congestive heart failure, particularly those with ejection fraction below 35%; patients with recent myocardial infarction or cerebrovascular accident within the past 6 months; and patients with unstable angina.

In addition, withdrawal of antihypertensive medications would be problematic in patients with orthostatic hypertension. Kario and colleagues<sup>17</sup> reported that among 110 asymptomatic elderly hypertensive patients without treatment, 7.2% had orthostatic hypertension, defined as a rise in SBP  $> 20$  mm Hg during a 70° head-up tilt.

#### CONCLUSIONS

There is an urgent need for clinical trials to examine the feasibility of taking selected very old patients off their antihypertensive medications. These studies could be initiated on those older individuals with OH. We plan to conduct a randomized trial in patients treated with antihypertensive drugs and with OH, in which half of the patients will remain on treatment and half will have treatment withdrawn and then followed for endpoints. The studies would have to be conducted cautiously in selected patients with frequent monitoring of BPs and reinstatement of antihypertensive medications if hypertension is detected. Outcome measures include mortality, hospitalization, medication costs, cardiovascular and cerebrovascular events, and cognitive functioning. The high incidence of mortality and morbidity in this population should provide adequate data with relatively low numbers of subjects tested. We believe that these clinical trials are an important first step in reducing polypharmacy and preventing morbidity and mortality related to the overuse of medications in the elderly.

*Acknowledgements and disclosure: The authors thank Drs Jacob Brody and Evan Hadley for their suggestions. The authors have no conflict of interest to declare.*

#### REFERENCES

- 1 Arias E. United States Life Tables, 2004. In: *National Vital Statistics Reports*. Vol. 56, No. 9. December 28, 2007. Table 10.
- 2 *Projections of the Population by Age and Sex for the United States: 2010 to 2050*. Population Division, U.S. Census Bureau; Release Date: August 14, 2008. Table 12.
- 3 Budnitz DS, Shehab N, Kegler SR, et al. Medication use leading to emergency department visits for adverse drug events in older adults. *Ann Intern Med*. 2007;147:755-765.
- 4 Beckett NS, Peters R, Fletcher AE, et al., for the HYVET Study. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med*. 2008; 358:1887-1898.
- 5 Bogousslavsky J, Hennerici MG, Kaste M, et al. The Mannheim declaration of stroke in Eastern Europe. *Cerebrovasc Dis*. 2004;18:248.
- 6 SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA*. 1991;265:3255-3264.
- 7 Yusuf S, Teo KK, Pogue J, et al. and the ONTARGET Investigators. Telmisartan, ramipril, or both in patients at

- high risk for vascular events. *N Engl J Med.* 2008; 358:1547–1559.
- 8 Kagiya S, Fukuhara M, Ansai T, et al. Association between blood pressure and mortality in 80 year old subjects from a population-based prospective study in Japan. *Hypertens Res.* 2008;31:265–270.
  - 9 Satish S, Freeman DH, Ray L, et al. The relationship between blood pressure and mortality in the oldest old. *J Am Geriatr Soc.* 2001;49:367–374.
  - 10 Langer R, Criqui MH, Barrett-Connor EL, et al. Blood pressure change and survival after 75. *Hypertension.* 1993;22:551–559.
  - 11 Port S, Demer L, Jennrich R, et al. Systolic blood pressure and mortality. *Lancet.* 2000;355:175–180.
  - 12 Euser SM, van Bommel T, Schram MT, et al. The effect of age on the association between blood pressure and cognitive function later in life. *J Am Geriatr Soc.* 2009; 57:1232–1237.
  - 13 Rutan GH, Hermanson B, Bild DE, et al. Orthostatic hypotension in older adults. The Cardiovascular Health Study. CHS Collaborative Research Group. *Hypertension.* 1992;19(6 Pt 1):508–519.
  - 14 Ooi WL, Barrett S, Hossain M, et al. Patterns of orthostatic blood pressure change and their clinical correlates in a frail, elderly population. *JAMA.* 1997;277:1299–1304.
  - 15 Hiitola P, Enlund H, Kettunen R, et al. Postural changes in blood pressure and the prevalence of orthostatic hypotension among home-dwelling elderly aged 75 years or older. *J Hum Hypertens.* 2009;23:33–39.
  - 16 Masaki KH, Schatz IJ, Burchfiel CM, et al. Orthostatic hypotension predicts mortality in elderly men. The Honolulu Heart Program. *Circulation.* 1998;98:2290–2295.
  - 17 Kario K, Eguchi K, Nakagawa Y, et al. Relationship between extreme dippers and orthostatic hypertension in elderly hypertensive patients. *Hypertension.* 1998;31:77–82.