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Hypertension in the Elderly

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From 2001 to 2002, among those 65 years of age and over, 47% of men and 52% of women reported having hypertension. The National Health and Nutrition Examination Survey (NHANES) suggests that among 65- to 74-year-olds, 60.9% of men and 74% of women are hypertensive. Among those 75 years and older, the numbers are 69.2% for men and 83.4% for women [1]. Together with the impending demographic wave (over the next 45 years, the "over 65" population in the United States will double and the "over 85" population will nearly quadruple) [2], high blood pressure (BP) will represent a major challenge to health care providers in this country. Hypertension is more prevalent in elderly women than elderly men and more prevalent in blacks compared with whites (Table 1), with data from the Center for Health Statistics indicating that between 1979 and 1997, death rates related to hypertension rose in elderly white women and in blacks of both sexes [3,4].

Prevalence in the Elderly

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) classification of BPs is outlined in Table 2 [5].

Among older adults with hypertension, isolated systolic hypertension (elevated systolic BP [SBP] with normal diastolic BP [DBP]) predominates over diastolic or combined systolic/diastolic hypertension (Table 3).

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Table 1
Prevalence of high blood pressure by sex and race among persons over 70 years of age

Group	BP ≥140/90 (%)
Black women	82.9
Black men	67.1
White women	66.2
White men	59.2

Data from Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population: results from the Third National Health and Nutrition Examination Survey, 1988–1991; and Hypertension 1995;25:305–30.

Even when those who have clinical cardiovascular disease or who take antihypertensive agents are excluded, hypertension is more likely to be isolated systolic hypertension, especially in women. By age 80 years, the prevalence of isolated diastolic hypertension is less than 4% [6], and in elderly nursing home residents, isolated diastolic hypertension is even more uncommon (<1%) [7]. Sagie and colleagues [8] reported that among untreated hypertensive patients aged 60 years and older, 76% of men with what is now classified as stage I isolated systolic hypertension will progress to stage II or higher, as will 47% of men whose SBP is less than 140 mm Hg at baseline. Among women, the numbers are 80% and 59%, respectively [8].

In contrast, findings from the Helsinki Aging Study suggest that although SBP increases with age in cross-sectional data, analysis of longitudinal data suggests that BP declines in most individuals at all entry ages (65, 75, 80, and 85 years), with 85-year-old men the only group to have less than half of the individuals experience a drop over the subsequent 5 years. Baseline BP was the single greatest predictor of subsequent decline (explaining 27%–37% of the variance). Baseline BP, age, health status after 5 years, a drop in cholesterol, and a drop in triglycerides were significant predictors of subsequent decline in BP readings [9].

Despite the well-established impact of high BP on health outcomes, a substantial segment of hypertensive patients remains unaware, untreated,

Table 2
Classification of blood pressures

BP classification	Systolic BP (mm Hg)		Diastolic BP (mm Hg)
Normal	<120	And	<80
Prehypertension	120–139	Or	80–89
Stage 1 hypertension	140–159	Or	90–99
Stage 2 hypertension	≥160	Or	≥100

JNC 7 classification.

Data from Chobanian AV, Bakris GL, Balck HR, et al. The Seventh Report of the The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. JAMA 2003;289:2561.

Table 3
Prevalence of systolic, diastolic, and combined high blood pressure

Group	Isolated systolic	Isolated diastolic	Systolic + diastolic
Men	58%	12%	30%
Women	65%	7%	28%

Adapted from Wiling SVB, Belanger A, Kannel WB, et al. Determinants of isolated systolic hypertension. JAMA 1998;260:3452.

or uncontrolled, with older Mexican American women being the least likely to achieve BP control (Table 4) [10]. Although data from 1999 suggest that over 97% of elderly report having had their BP checked and increasing numbers report having hypertension [11], awareness, knowledge, and attitudes about high BP may be barriers to effective therapy. A nationally representative sample of 1503 adults over age 50 years revealed that only 55% recognized that hypertension and high BP were the same. Only 30% identified hypertension as a serious health concern. Although most had had their BP measured, only 54% knew their BP [12].

Among elderly patients who have uncontrolled hypertension, 80% have isolated systolic hypertension and an additional 14% meet systolic and diastolic criteria [13]. Among elderly persons from the NHANES-III who

Table 4
Awareness, treatment, and control of high blood pressure

Group	% Aware	% Treated	% Controlled
Non-Hispanic blacks			
Men			
50–69 y	73	56	22
70+ y	67	58	25
Women			
50–69 y	84	71	29
70+ y	79	70	23
Non-Hispanic whites			
Men			
50–69 y	71	55	25
70+ y	56	46	16
Women			
50–69 y	81	66	34
70+ y	68	58	19
Mexican Americans			
Men			
50–69 y	54	37	15
70+ y	55	40	12
Women			
50–69 y	70	47	16
70+ y	49	31	7

Data from Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population: results from the Third National Health and Nutrition Examination Survey, 1988–1991. Hypertension 1995;25:305–13.

were unaware of their high BP, 91% had isolated systolic hypertension. The elderly were nearly 8 times as likely to be unaware of their hypertension and nearly twice as likely not to have achieved control even after they were aware [14]. Among elderly nursing home residents with a mean age of 83 ± 8 years, hypertension is listed as a diagnosis on the federally required Minimum Data Set in 32% of patients. Prevalence was higher among women (33%) than men (27%), and among African Americans (43%) and other minorities (34%) compared with whites (30%). With advancing age, the prevalence decreased: 35% in 65- to 74-year-olds, 33% in 75- to 84-year-olds, and 30% in those 85 and older, although most of this difference was accounted for by a decline in the percentage in African American men because prevalence was not affected by age in women. Many patients had comorbidities: 26% had coronary artery disease, 22% had congestive heart failure, and 29% had cerebrovascular disease [15].

Dietary, medication, and environmental factors

Dietary sodium intake is a well-established risk factor for the development of hypertension, whereas increased dietary calcium has been shown in the NHANES-III cohort to be associated with a blunting of the age-related increases in SBP and pulse pressure [16,17]. Potassium intake is associated with lower SBP and DBP, whereas alcohol intake is associated with only lower DBP. In addition, the age-related changes in SBP are attenuated by higher protein intake. Magnesium is not associated with any changes in BP [17].

Gurwitz and colleagues [18] reported that elderly patients on nonsteroidal anti-inflammatory drugs (NSAIDs) are at increased risk for subsequent hypertension. In looking at Medicaid enrollees 65 years old and older in New Jersey, these investigators found that the odds ratio for subsequent initiation of antihypertensive therapy was 1.66 (95% confidence interval [CI]: 1.54–1.80) and was NSAID-dose related. Similar trends were reported by Johnson and coworkers [19] in a meta-analysis not limited to the elderly. Pooled data from randomized placebo-controlled trials revealed that NSAIDs elevated mean BP by 5 mm Hg (95% CI: 1.2–8.7), with no statistically significant difference in the elevation according to antihypertensive drug class or NSAID type (although there was a trend toward greater elevations in patients on β-blockers or vasodilators compared with those on diuretics). In somewhat younger patients (mean age, 50 years), Coates and colleagues [20] reported that pseudoephedrine, found in over-the-counter cold remedies and often listed as an agent that may exacerbate high BP, had no effect on BP or pulse rate when administered at a dose of 60 mg four times a day. Given that elderly patients have a tendency toward blunted α-adrenergic responsiveness [21], it is unlikely that pseudoephedrine in the usual clinical dose has a meaningful effect on the BP of most elderly

hypertensive patients. Pseudoephedrine and similar drugs, however, may precipitate urinary retention in elderly men who have prostatic hypertrophy.

Lead exposure has also been shown to be a risk factor for hypertension in postmenopausal women, although not specifically in the elderly [22]. Data from the Framingham Heart Study suggest that in women, obesity in midlife may predict the subsequent development of isolated systolic hypertension [23].

Findings of the Baltimore Longitudinal Study on Aging support an association between an attenuation of the age-related increase in SBP and hormone replacement therapy. For women who were age 65 years at entry, 10 years of hormone replacement therapy was associated with a 6.6 mm Hg rise in SBP compared with a 25.6 mm Hg rise in nonusers [24]. Findings from the Women's Health Initiative, however, raise concern about the safety of hormone replacement therapy.

Among obese individuals, the risk for all-cause mortality appears to increase as body mass index increases, especially for those who also have a high sodium intake. There also appears to be an increased risk of fatal stroke in this group [25].

Finally, genetic predisposition and sleep apnea may play a role in the development of hypertension. Strazzullo and colleagues [26] suggested that DD homozygous polymorphism in the angiotensin-converting enzyme (ACE) gene angiotensinogen M235T may be a risk factor for increasing BP in aging persons. Sleep apnea has also been linked to hypertension, although the association appears to be weaker in those over the age of 80 years [27,28].

Age-related physiologic changes impacting blood pressure and blood pressure regulation

Studies of aging have demonstrated steady increases in mean brachial artery pressure beginning in young adulthood and continuing into the eighth decade, although there are differences between populations in the magnitude of the increase. For example, the increase in a rural population was substantially less than that observed in an urban population [29]. Dilatation of the aorta and large arteries, thickening of arterial walls, increased number of collagen fibers in the arterial wall, decreased glycoprotein content of elastic fibrils, increased mineralization ($CaPO_4$) of the elastin, and increased left ventricular posterior wall diastolic thickness are seen with normal aging [29,30]. Functional changes, including increased arterial wall tension, increased peripheral resistance, and an increased arterial stiffness (even in the absence of overt hypertension), manifest as an increased arterial pulse wave velocity [31], which results in the reflected pulse wave returning sooner. In the elderly, the wave reaches back to the thoracic aorta before the left ventricular ejection period has ended, resulting in a summation of the waves, an increase in the SBP, and workload on the left ventricle [32]. Berry and

colleagues [33] reported that independent of other known confounders, older women with hypertension have stiffer large arteries, greater central wave reflection, and higher pulse pressures than older hypertensive men, despite higher mean arterial pressure in men. The investigators postulated that this may partly explain the postmenopausal acceleration in the rate of cerebrovascular and cardiac complications.

Aging is associated with declines in carotid baroreceptor function and β-adrenergic receptor–mediated vascular relaxation and chronotropic response but with preserved response to nitroglycerin [34,35].

Effect of hypertension on cardiovascular physiologic changes of aging

Among those with established hypertension, older patients tend to have higher total peripheral resistance, lower cardiac index and left ventricular ejection rate, lower plasma renin activity, lower central and total blood volume, and lower renal blood flow compared with younger hypertensive patients [35–37]. Older patients who have hypertension do not appear to have the normal age-related increase in sympathetic nervous system activity (as reflected by plasma norepinephrine levels), and cardiopulmonary baroreceptor function that is diminished by hypertension is not further diminished in older patients who have hypertension [38]. In contrast, β-adrenergic receptor responsiveness and baroreceptor sensitivity exhibit modest declines beyond that occurring from aging alone [35,39].

Does high blood pressure have adverse effects in elderly persons?

Epidemiologic evidence from the Framingham Heart Study suggests that hypertension is associated with an increased risk of developing cardiovascular disease, with the risk per millimeter-of-mercury rise in SBP increasing with advancing age, at least through age 70 years [40]. Findings from the Cardiovascular Health Study (community-dwelling elderly aged 65 years and older; average age, 72 years) demonstrate an association between SBP and EKG evidence of myocardial infarction, left ventricular mass, and diastolic (but not systolic) cardiac function. Isolated systolic hypertension is also strongly associated with increased intima-media thickness of the carotid artery [6], and reported to be associated with a high risk of carotid bruit [41]. The risk of cardiovascular disease rises proportionally with increasing DBP above 85 mm Hg in older men; however, this trend is reportedly blunted in older women, with increased risk appearing only after DBPs exceed 104 mm Hg [42]. In a meta-analysis of outcome trials in isolated systolic hypertension (SBP >160 mm Hg and DBP <95 mm Hg) in patients over age 60 years, Staessen and colleagues [43] reported that although increasing SBP was associated with increased relative hazard rates for total mortality (relative risk [RR] $= 1.26$ for each 10–mm Hg increase, $P = .0001$)

and stroke (RR = 1.22 for each 10–mm Hg increase, $P = .02$), the relative risk of coronary events (RR = 1.07 for each 10–mm Hg increase, $P = .37$) was not significantly increased. These investigators also observed an inverse relationship between DBP and mortality. Likewise, 10-year follow-up of the Studio sulla Pressione Arteriosa nell'Anziano study in Italy revealed that SBP (but not DBP) is a strong positive, continuous, independent predictor of total mortality and cardiovascular mortality, even in patients older than 75 years [44]. In addition, the Rotterdam Study demonstrated that 1 SD increase in SBP was associated with a 24% increased risk of myocardial infarction, a 59% increased risk of stroke, and a 21% increased risk of all-cause mortality. Increases (1 SD) in DBP had no statistically significant effect on myocardial infarction or all-cause mortality, and had a lesser (27% increase) effect on stroke risk [45]. Furthermore, at least for those in their 60s and 70s, midlife BP appears to impact the risk of stroke from any given level of current BP [46].

Congestive heart failure

High BP is also a known risk factor for the development of congestive heart failure. Framingham Heart Study follow-up at an average of 17 years revealed that a 20–mm Hg increase in SBP produced a 56% increase in the risk of congestive heart failure. Although DBP also predicted subsequent heart failure, it was a much weaker predictor than SBP or pulse pressure. Separate analysis restricted to patients over age 60 years on entry revealed that this relationship was present. Time-dependent systolic pressure, but not time-dependent diastolic pressure, predicted development of heart failure [47].

Progression of atherosclerosis

Progression of carotid and aortic atherosclerosis is also predicted by high BP. In the Rotterdam Study, SBP (but not DBP) was predictive of progression of atherosclerotic carotid plaques, carotid intima-media thickness, aortic atherosclerosis, and lower-extremity atherosclerosis (assessed by decline in the ratio of the SBP at the ankle to the SBP in the arm [ankle/arm BP index]) [48].

Age-related maculopathy

The risk of age-related maculopathy has been shown to increase with increasing SBP. In the Rotterdam study, each 10–mm Hg increase in SBP was associated with an 8% increase in the odds of age-related maculopathy (odds ratio = 1.08, 95% CI: 1.03–1.14) [49].

Effect of high blood pressure on cognition

Hypertension appears to have a negative impact on cognition, although findings are not entirely consistent from study to study. Among young

elderly (mean age, 72 years), Kuo and colleagues [50] reported that each 10–mm Hg increase in supine SBP was associated with a 2.31-fold increased risk of impairment in psychomotor speed and set shifting, although there was no impact on tests of verbal fluency, memory, or visuospatial functions. Wallace and coworkers [51] reported that free recall memory was decreased among elderly patients with diastolic (but not systolic) hypertension. Glynn and colleagues [52] found that although current BP was not well correlated with cognitive functioning, BP from 9 years before cognitive testing demonstrated a U-shaped association with the number of errors on memory testing (Short Portable Mental Status Questionnaire). Error rates were 9% higher in patients with SBP less than 130 mm Hg and 7% higher among those with SBPs of 160 mm Hg or greater. Petitti and coworkers [53] reported that retrospective review of charts of patients who had dementia revealed that systolic pressures increased less over time in those who eventually developed dementia, and the diastolic drop that was seen over time in all groups was the most pronounced among those eventually developing dementia. de Leeuw and colleagues [54] reported that duration of hypertension correlated with the volume of periventricular and subcortical white matter lesions seen on MRI. The Cardiovascular Determinants of Dementia study reported that among 65- to 75-year-olds, current and previous BP (SBP and DBP) were predictive of severe subcortical and periventricular white matter lesions. In addition, although more rapid increases in systolic pressure over time were predictive of subcortical and periventricular severe white matter changes, these changes were seen with increases and decreases in diastolic pressure compared with prior readings [55]. Sacktor and colleagues [56] compared hypertensive patients by degree of BP control and found that compared with those who had a mean SBP of 135 to 150 mm Hg, those who had an SBP of 135 mm Hg or less had accelerated memory decline (particularly delayed recall), as did those who had an SBP greater than 150 mm Hg (particularly free recall). In the Systolic Hypertenion in the Elderly Program (SHEP) trial, dementia developed in 1.6% of the intervention group versus 1.9% of the placebo group (but one third of the placebo group were on active treatment by year 3) [57].

In the Systolic Hypertenion in Europe (Syst-Eur) trial, Mini-Mental State Exam scores decreased with decreasing diastolic pressures ($P = .04$) in the placebo group but not in the active treatment group. In addition, active treatment of systolic hypertension in this trial was associated with a 50% reduction in the incidence of dementia [58]. Open-label extension of the trial revealed that compared with the controls, long-term antihypertensive therapy reduced the risk of dementia by 55%, from 7.4 to 3.3 cases per 1000 patient years (43 versus 21 cases, $P < .001$). After adjustment for sex, age, education, and entry BP, the relative hazard rate associated with the use of nitrendipine was 0.38 (95% CI: 0.23–0.64, $P < .001$). The data suggest that treatment of 1000 patients for 5 years could prevent 20 cases of dementia (95% CI: 7–33) [59]. Finally, in the Rotterdam Study, antihypertensive therapy resulted in

a decreased risk of vascular dementia (adjusted RR 0.3, 95% CI: 0.11–0.99) and an insignificant 13% reduction in Alzheimer's disease [60].

Circadian variation in blood pressure

Blood pressure varies over the course of the day. Among younger nonhypertensive and hypertensive individuals, BP is usually lowest in the early morning hours, peaks in the afternoon, and then begins to decline [61]. Variations in the timing and magnitude of circadian variation have been associated with increased pathology, although findings have not necessarily been consistent. Using ambulatory BP monitoring, Pasqualini and colleagues [62] demonstrated that elderly patients whose nighttime decrease in BP was less than 10% ("nondippers") tended to have poorer quality of sleep and were more likely to be using benzodiazepines. Among 131 asymptomatic elderly patients who had hypertension but not pre-existing cerebrovascular disease, diabetes, or renal insufficiency, Kario and coworkers [63] reported that the prevalence of silent cerebrovascular insults was lowest in patients whose nighttime reduction was between 10% and 20% but was comparably elevated in nondippers (nighttime BP decreased $<10\%$) and in extreme dippers (nighttime BP decreased $\geq 20\%$). Left ventricular hypertrophy and microalbuminuria were more prevalent only in nondippers. In contrast, Nakamura and colleagues [64] demonstrated that among patients who already had cerebrovascular disease and who were on antihypertensive therapy, recurrent stroke and the development of new silent ischemic lesions on MRI were (1) more common in those whose nighttime mean arterial BP was at least 10 mm Hg lower than the daytime mean arterial BP compared with individuals on treatment whose day–night difference was less than 10 mm Hg, and (2) comparable to individuals who remained untreated for hypertension.

Patient evaluation

The JNC 7 recommends that physical examination should (1) include at least two measurements of BP with a properly calibrated and validated instrument of appropriate cuff size, (2) be performed with the patient seated with feet on the floor and arm supported at heart level, and (3) use the auscultatory method [5]. The JNC 7 further recommends that SBP be defined as the point at which the first of two or more sounds is heard (phase 1) and DBP as the point before the disappearance of sounds (phase 5), and that the readings and the goal BPs be provided verbally and in writing to the patient. If Korotkoff's sounds disappear and then reappear during cuff deflation, this presence of an auscultatory gap should be noted. An auscultatory gap is more common in the elderly and associated with increased arterial stiffness and an increased prevalence of carotid

atherosclerosis [65]. It should be noted that in elderly persons and in those who have isolated systolic hypertension or peripheral atherosclerosis, cuff DBPs are consistently higher than intra-arterial readings by 10 to 18 mm Hg [32,33]. Cuff measurement of SBPs in elderly patients has been reported to underestimate by 4 to 7 mm Hg [34] and insignificantly overestimate intra-arterial readings [33]. When excessive atherosclerosis is present, however, it may require pressure simply to compress the artery, independent of the actual intra-arterial BP, leading to spurious elevations in indirect sphygmomanometric readings (often referred to as pseudohypertension). When pseudohypertension is suspected (eg, with disproportionate symptoms after modest lowering of BP), one should consider performing Osler's maneuver or obtaining BP using an automated device that uses the infrasonic recorder method. Osler's maneuver is performed by assessing the palpability of the pulseless radial or brachial artery distal to the cuff occlusion after the cuff is inflated above systolic pressure. When either of these arteries is palpable with the cuff inflated above systolic pressure, Osler's maneuver is said to be positive. In Osler-positive patients, mercury sphygmomanometry overestimates BP by 10 to 54 mm Hg [35]. The infrasonic recorder may be more accurate in reflecting intra-arterial pressure. Hla and Feussner [66] reported that an infrasonic recorder-cuff difference of 4 mm Hg or greater is sensitive in detecting patients whose cuff reading is greater than 10 mm Hg above their intra-arterial reading. The method is only moderately specific, however, and requires confirmation with direct intra-arterial measurement.

Recording of phases 1, 4, and 5 has been advocated in patients in whom there is a large difference between phase 4 (muffling of Korotkoff's sounds) and phase 5 (disappearance of Korotkoff's sounds), in patients who have hyperthyroidism or aortic insufficiency, and in patients after exercise [67].

Common errors in indirect BP measurement include observer bias, faulty equipment, and failure to standardize the measurement technique [67]. A full review of this subject is beyond the scope of this article. Readers interested in more details about specific measurement issues are referred to (www.nhlbi.nih.gov/health/prof/heart/hbp/bpmeasu.pdf). In the authors' experience, errors commonly encountered in practice include not palpating the brachial artery to ensure that the cuff has been inflated above systolic pressure (rather than into the auscultatory gap), not raising the arm to the level of the heart, and terminal digit preference (most commonly for 0 or 5), which may be avoided by use of an automated device [68]. Practitioners are reminded to calibrate aneroid devices periodically because one study reported that up to 80% of aneroid sphygmomanometers at university hospitals and clinics were found to yield unreliable measurements [69].

In addition, in interpreting BP measurements, clinicians should be aware of the normal decline in pressure that occurs after meals in elderly patients, typically most pronounced within the first hour [70] and more pronounced

in hypertensive elderly patients. Postprandial declines of 10 mm Hg or greater are reportedly associated with an increased risk of leukoariosis and lacunar infarction [71], and postprandial readings below 115 mm Hg systolic in frail elderly have been reported to be associated with falls [72].

At the initial visit and on subsequent visits when prompted by symptoms or the addition of medications that increase the likelihood of orthostatic hypotension, measuring BP after the patient is supine for at least 5 minutes and then after standing for 1 to 2 minutes may be useful. Orthostatic hypotension is a risk factor for falls, syncope [73,74], and stroke [75]. Orthostatic declines in diastolic pressure predict cardiovascular mortality [76]. Despite concern over the potential of aggravating the orthostatic changes, cautious treatment of hypertension appears to decrease the likelihood of orthostasis [77].

Although not advocated by the JNC 7 as part of the routine assessment, where available, Doppler BP in all four extremities may be worth consideration at the initial visit. This methodology allows calculation of the ankle/arm BP index, which has been demonstrated to be a sensitive and specific marker of peripheral vascular disease in the elderly, predictive of survival [78], and a predictor of carotid arterial disease among those who have isolated systolic hypertension [79].

As recommended by the JNC 7, initial evaluation of the patient with hypertension should include physical examination, routine laboratory studies, and further diagnostic procedures as indicated after the initial evaluation. Although the utility of most of the individual components of the examination has not been well documented, in addition to an appropriate measurement of BP in both arms, initial physical examination should include height and weight (to calculate body mass index); auscultation for carotid, femoral, and abdominal bruits; and palpation for the presence of an abdominal aortic aneurysm. Funduscopic examination should be performed to determine the presence of hypertensive retinal changes and to assess for the presence of age-related macular degeneration that is more prevalent in elderly hypertensive patients [49]. Palpation of the abdomen should seek to detect enlarged kidneys or masses. Palpation of the thyroid, a thorough examination of the heart and lungs, and a neurologic examination including a baseline cognitive assessment should be performed. Finally, the presence of edema and the status of the peripheral pulses should be noted.

The JNC 7 advises that routine diagnostic studies at initial evaluation should include EKG, serum potassium, creatinine, glucose, calcium, hematocrit, lipid profile, and a urinalysis. In the SHEP trail, participants with baseline EKG abnormalities experienced a greater percentage reduction in subsequent cardiovascular events with treatment than did those with normal EKG at baseline [57]. Assessment of concomitant obesity and hyperlipidemia is advised as noted previously, with the caveat that at advanced age, total cholesterol no longer adds predictive value. In the European Working Party on High Blood Pressure in the Elderly trial, the

association of body mass index with outcomes depends on age, treatment status, and the outcome variable of interest, such that no particular ideal body mass index can be comfortably derived from the data. Patients whose body mass indexes were slightly above the population mean of 27 kg/m^2 had the lowest risks [80] and, independent of other risk factors and treatment, mortality in this cohort decreased 14% for each 1-mmol/L increase in pretreatment serum total cholesterol [81]. Additional studies should be guided by results of the initial evaluation or the presence of difficult-to-control BP.

Although not a JNC 7 recommendation, an echocardiogram may be more reliable than an EKG to evaluate left ventricular hypertrophy. In patients who show left ventricular hypertrophy on echocardiogram, consideration should be given to obtaining a urinary albumin/creatinine ratio. This ratio has been shown in diabetic and nondiabetic elderly to predict increasing risk for cardiovascular morbidity and mortality among hypertensive patients who have left ventricular hypertrophy [82].

What is the role for ambulatory blood pressure monitoring in the elderly?

Ambulatory BP monitoring is not routine for elderly patients. Using participants of the Syst-Eur trial, Staessen and colleagues [83] reported that ambulatory BP monitoring in elderly patients with untreated systolic hypertension adds to the ability to predict mortality, cardiac events, and stroke. Nighttime BP (12 AM–6 AM) more accurately predicted end points than daytime level. Untreated patients with a 10% increase in their night/day ratio were 41% more likely to experience an event. Among treated patients, the additional predictive power was lost.

Because all of the major intervention trials for hypertension in the elderly used seated BP as their standard measurement, clinicians using ambulatory monitors should recognize that average 24-hour BP readings correlate less well with casual SBP readings in the elderly (young, $r = 0.69$; elderly, $r = 0.42$) and that casual readings have been reported to run 17 to 28 mm Hg higher than 24-hour average readings with ambulatory monitors [61,83,84]. Clinic–ambulatory differences are higher with advancing age and increasing clinic SBP [84]. For a discussion of technical issues with ambulatory monitors, the reader is referred to www.nhlbi.nih.gov/health/prof/heart/hbp/bpmeasu.pdf.

What is the significance of ''labile hypertension''?

Although ''labile hypertension'' is often believed to have less clinical significance than ''fixed hypertension,'' data from the Framingham Heart Study cohort demonstrated that within-person variation of SBP increases steadily with advancing age. Although labile hypertension is associated with an increased risk of cardiovascular disease, multivariate analysis considering

age and baseline BP reveals that lability of pressure is not an independent predictor of cardiovascular risk. Clinicians are advised to not simply accept the lowest of several office BP readings but to calculate the average of the readings [85].

Can the clinician base treatment on self-recorded blood pressure monitoring when the patient has difficulty making it to the office for blood pressure checks?

Although done by many physicians and endorsed by the JNC 7 as potentially benefiting patients by providing information on response to antihypertensive therapy, by improving medication adherence, and in evaluating the possibility of white-coat hypertension [5], the practice benefit of having elderly patients record their own BP at home is unproved. There are little data on the accuracy and predictive value of this practice in the elderly. Although one study in patients with a mean age of 61 years in rural Japan demonstrated that ambulatory SBP readings were more predictive of subsequent mortality than office SBPs [86], another report from that study indicated that isolated systolic hypertension (mean age of subjects, 71.6 years) did not reach statistical significance in predicting cardiovascular disease mortality rate (relative hazard = 1.49, 95% CI: 0.89–2.47, $P = .13$) [87]. Furthermore, Hitzenberger and Magometschnigg [88] reported that self-monitoring is not associated with improvement in the number of patients achieving normotension.

A meta-analysis of studies examining self-reported BPs (largely in younger patients) suggested that a self-recorded SBP of 125 mm Hg was equivalent to a conventional office BP of 140 mm Hg, and a self-recorded DBP of 79 mm Hg corresponded to a conventional reading of 90 mm Hg [89]. Turnbull and colleagues [90], however, reported that patient self-recorded BPs using an automated oscillometric device were 4.7 (SBP) and 2.7 (DBP) mm Hg higher than those recorded by a trained nurse using the automated device or a standard mercury sphygmomanometer. Studies in younger hypertensive patients have demonstrated that left ventricular hypertrophy remains substantially more common in patients whose office BPs are elevated compared with those who are at target BP, despite similarly controlled home BPs [91]. For a discussion of technical issues related to home BP monitoring, the reader is referred to www.nhlbi.nih.gov/health/prof/heart/hbp/bpmeasu.pdf.

Treatment

Thijs [92] observed the increasing effect of placebo on BP reductions with advancing age and noted the necessity for placebo-controlled trials to assess the effect of age on therapeutic responses. There is evidence in the elderly that pharmacologic and nonpharmacologic interventions may be beneficial.

Nonpharmacologic treatment

Several studies have suggested that hypertension in elderly patients is more sensitive to dietary sodium intake [93–96]. Geleijnse and colleagues [97] reported that a sodium:potassium:magnesium (8:6:1) salt substitute used at the table and in food preparation resulted in a 7.6/3.3–mm Hg reduction in BP in the salt substitute group compared with controls who used common table salt, and produced a 28% decrease in urinary sodium excretion. It should be noted that although the elderly are more likely to be salt sensitive, BP may increase in some patients in response to sodium restriction [98]. In addition, a potentially unintended consequence of dietary salt restriction may be decreased iodine intake because in many communities, iodized salt constitutes a major source of iodine intake [99].

Potassium supplementation has inconsistently shown small hypotensive effects; however, there is insufficient evidence in the elderly to make a specific recommendation. Encouragingly, higher intake of potassium is associated with a reduction in stroke-associated mortality, independent of other known cardiovascular risk factors [100,101].

In a small trial, Applegate and colleagues [102] reported that a multifactorial nonpharmacologic intervention (weight reduction, sodium restriction, and exercise) in patients (average age, 65 years) reduced BP by 4.2/4.9 mm Hg compared with controls. In perhaps the largest randomized, controlled trial of nonpharmacologic interventions in the elderly, Whelton and coworkers [103] reported that among subjects 60 to 80 years old whose BP was less than 145/85 mm Hg at entry, sodium restriction (hazard ratio [HR] = 0.69, 95% CI: 0.59–0.81, $P < .0010$) and weight loss in obese persons (HR = 0.70, 95% CI: 0.57–0.87, $P < .001$) resulted in lower use of BP medication, fewer new diagnoses of hypertension, and fewer cardiovascular events.

Biofeedback has also been explored as a nonpharmacologic option in the elderly, but no outcome trials are available. A small study in elderly patients with isolated systolic hypertension revealed a modest decline in BP. Average monthly professionally measured BP fell significantly, from 164.7/87.1 to 156.9/81.5 mm Hg [104].

Finally, although no intervention data are available specifically in the elderly, smoking has been demonstrated to be associated with an increased risk of coronary heart disease, and the increased risk has been shown to decline to nonsmoker levels within 1 to 5 years after cessation [105].

Pharmacologic treatment

There are several major studies that have focused on elderly patients or included them as a substantial component of the study cohort (Table 5). Choice of initial agent depends on the presence or absence of "compelling indications." For example, the JNC 7 recommends that for patients who have heart failure, diuretics, β-blockers, ACE inhibitors, angiotensin

receptor blockers, and aldosterone antogonists are all accepted therapeutic agents. For patients who have sustained a myocardial infarction, β-blockers, ACE inhibitors, and aldosterone antogonists are recommended. For patients who have diabetes, all of these agents except angiotensin receptor blockers are advised. For patients who have chronic kidney disease, ACE inhibitors and angiotensin receptor blockers are recommended. For patients who have had a stroke, diuretics and ACE inhibitors are suggested [5].

A Department of Veterans Affairs Cooperative Study demonstrated that 78% of patients could achieve target BP results with 25 mg of hydrochlorthiazide, and 89% with 50 mg daily [106]. SHEP reported no difference in the benefit achieved when analyzed by age, race, or sex [107]. In a meta-analysis of outcome trials in isolated systolic hypertension (SBP $>$ 160 mm Hg and DBP $<$ 95 mm Hg) in patients over age 60 years, Staessen and colleagues [43] reported that treatment was associated with a 13% reduction in total mortality (95% CI: 2–22, $P = .02$), an 18% reduction in cardiovascular mortality, a 26% reduction in cardiovascular complications, a 30% reduction in stroke, and a 23% reduction in coronary events. The number needed to treat for 5 years to prevent one major cardiovascular event was lower in patients over age 70 years (19 versus 39), in men (18 versus 38), and in those who had previous cardiovascular complications (16 versus 37). Hemorrhagic and ischemic strokes are reduced with therapy [108]. Beneficial effects have also been variously reported to include reductions in congestive heart failure [109], dementia [58–60], and left ventricular mass. Antihypertensive treatment had a favorable effect on left ventricular mass index (RR = 0.6, 95% CI: 0.4–0.9) regardless of whether treatment used ACE inhibitors, diuretics, β-blockers [110], or calcium channel blockers, with some suggestion that calcium channel blockers may have a greater effect than β-blockers [111].

Applegate and colleagues [112] evaluated the effect of various degrees of SBP control in patients whose ''on-treatment'' DBPs were less than 90 mm Hg. Compared with patients whose SBPs were at times greater than 160 mm Hg but averaged 151 mm Hg, those whose SBPs were consistently greater than 160 mm Hg (mean, 184 mm Hg) and those whose SBPs were always under 160 mm Hg (mean, 137 mm Hg) had higher cardiovascular morbidity and mortality rates, with rates 50% higher in the ''tighter control'' group compared with the ''moderate-control'' group.

Although the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial [113] has suggested the superiority of thiazide diuretics, the Second Australian National Blood Pressure Study suggested that ACE inhibitors may be more beneficial. The latter study included over 6000 patients (51% women) aged 65 to 84 years (mean age, 72 years) who had SBPs of 160 mm Hg or greater or DBPs of 90 mm Hg or greater, with those having SBPs of 140 mm Hg or greater randomized to ACE inhibitors or to diuretics as initial therapy. At 5 years, BP had decreased 26/12 mm Hg in both groups. The outcome (all cardiovascular events and all-cause mortality) rate was lower in patients allotted to the ACE inhibitor group

Table 5
Large trials of high blood pressure in the elderly

Study	Type of HTN	Age (y)	Exclusions	Entry BP (mm Hg)	Target BP (mm Hg)	Drugs	Significant outcomes
SHEP [57] (randomized, blinded, placebo-controlled)	S	60+	Variety of cardiac conditions; insulin; anticoagulants; dementia; Cr >2.0 mg/dL; COPD; EtOH abuse; cancer; life-threatening illness; live in nursing home	S >159 D <90	Lower of S <160 or 20 below baseline	Placebo versus chlorthalidone, then add 1 of: reserpine, metoprolol, hydralazine, or placebo	Stroke; CHF; CV events; CV mortality; dementia
EWPHE [139] (double-blinded, placebo-controlled)	C	60+	Curable causes of HTN; grade II or IV retinopathy; cerebral hemorrhage; hepatitis; cirrhosis; gout; cancer; IDDM	S = 160–239 D = 90–119	S <160 and D <90	HCTZ/triamterene, then add methyldopa	Total CV; total cardiac; MI
Syst-Eur [58,59] (randomized double-blinded)	S	60+	Standing SBP <140; secondary HTN; retinal hemorrhage or papilledema; CHF; dissecting AA; Cr >2 mg/dL; severe epistaxis; MI or CVA within 1 year; dementia, substance abuse; inability to stand; severe CV or non-CV disease	S = 160–219 D <95	S ≥20 below baseline or S <150	Nitrendipine, then add enalapril ± HCTZ	Total stroke; nonfatal stroke; nonfatal cardiac events; total cardiac events; total CV events; dementia

VA Cooperative Trial [106] (randomized, controlled)	D	30–69	Secondary HTN; a variety of medical conditions	D = 95–109	D ≤90	Stepped care versus referral to community care	All-cause mortality (subgroup age 60–69; $P = .08$)
Rotterdam Study [45,48,49,60,110] (prospective population-based cohort)	C	>55	Patients diagnosed with dementia at the time of enrollment	S ≥160 D ≤95	Observation	Not applicable (observation study)	Dementia; chronic disabling cardiovascular, neurologic, locomotor, and ophthalmologic diseases
LIFE [82] [randomized double-blinded parallel group]	E	55–80 with LVH	Secondary HTN; MI or CVA within 6 mo; angina requiring BB or CCB; CHF; EF <40%	S = 160–200 and/or D = 95–115	S ≤140	Losartan vs atenolol	Stroke; New DM (both favored by losartan); cardiovascular death
NORDIL [144] [prospective randomized, open, blinded endpoint]	D	50–74	Patients currently on anti-HTN Tx (unless met entry criteria at 2 visits 1 wk apart off meds)	D ≥100	D <90	Diltiazem, then ACEI, then AB versus diuretic and/or BB, then ACE, then AB	Total stroke (favored by diltiazem regimen)
STOP-II [145,146] (randomized, double-blinded, controlled; 6614 patients)	E	70–84	SBP >230 mm Hg; DBP >120 mm Hg; orthostatic SBP drop >30; MI or CVA in last year; angina requiring meds × NTG; severe/incapacitating illness	S ≥180 and/or D ≥105	<160/95	Conventional (atenolol, metoprolol, or HCTZ + amiloride) versus newer agents (enalapril, lisinopril, felodipine, or isradipine)	No differences in outcomes between "old" and "new" drugs

(*continued on next page*)

Table 5 (*continued*)

Study	Type of HTN	Age (y)	Exclusions	Entry BP (mm Hg)	Target BP (mm Hg)	Drugs	Significant outcomes
STOP-I [147] (randomized, double-blinded, controlled; 1627 patients)	E	70–84	SBP >230 mm Hg; DBP >120 mm Hg; SBP ≥180 but DBP <90; Orthostatic SBP drop >30 mm Hg; MI or CVA in the last year; angina requiring meds × NTG; severe/ incapacitating illness	180–230/ ≥90 or D: 105–120	S <160/95	Any of: atenolol, HCTZ + amiloride, metoprolol, pindolol, (then add other class if needed)	Stroke + death; total mortality
MRC [148] (randomized placebo-controlled, single-blinded)	B or S	65–74	Secondary HTN; on HTN meds; CHF; Tx for angina; MI or CVA in last 3 mo; renal insufficiency; DM; asthma, K ≤3.4 or >5.0	S: 160–209 and D: <115	S <150 (if entry S <180); S <160 if entry S = 180–209	Atenolol or HCTZ + amiloride or placebo	Stroke; CV events; (both favored by diuretic only)
ANBP-2 [114,149] (randomized [allocation concealed], blinded outcome assessors)	E	65–84	Life-threatening illness; Cr >2.5 mg/dL; malignant HTN; dementia	S: ≥160 or D: >90 (with S ≥140)	Decrease S by 20 or <140, and decrease D by 10 or <90	ACEI or diuretic for initial Tx (at discretion of PMD)	CV events + all-cause mortality (favored ACEI)

Abbreviations: AA, aortic aneurysm; AB, alpha blocker; ACEI, ACE inhibitor; ANBP-2, Second Australian National Blood Pressure Study; B, both systolic and diastolic hypertension; BB, β-blocker; CCB, calcium channel blocker; CHF, congestive heart failure; Cr, creatinine; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; CVA, cerebrovascular accident; D, diastolic; DM, diabetes mellitus; E, either systolic or diastolic hypertension; EF, ejection fraction; EtOH, alcohol; EWPHE, European Working Party on High Blood Pressure in the Elderly; HCTZ, hydrochlorthiazide; HTN, hypertension; IDDM, insulin-dependent diabetes mellitus; K, potassium; LIFE, losartan intervention for endpoint reduction in hypertension study; LVH, left ventricular hypertrophy; meds, medication; MI, myocardial infarction; MRC, Medical Research Council; NORDIL, Nordic Diltiazem study; NTG, nitroglycerin; PMD, primary medical doctor; S, systolic; STOP-I, Swedish Trial in Old Patients with Hypertension I; STOP-II, Swedish Trial in Old Patients with Hypertension II; Tx, treatment; VA, US Department of Veterans Affairs.

compared with the diuretic group (odds ratio = 0.89, 95% CI: 0.79–1.00). The difference in the number needed to treat was 3.7; however, the upper confidence limit of the number needed to treat was greater than 400, suggesting that although the difference was statistically significant, it was not likely clinically significant [114].

Special populations

Are diuretics effective in elderly patients who have mild renal dysfunction?

The SHEP trial investigators evaluated the effect of mild renal dysfunction on the effectiveness of chlorthalidone in treating systolic hypertension. Compared with patients who had normal creatinine, patients who had serum creatinine 1.35 to 2.40 mg/dL achieved similar BP reductions (with no additional deterioration in renal function) and were less likely to develop hypokalemia [115].

What evidence is there for benefit of treatment among elderly hypertensive patients who have diabetes?

Treatment of hypertension using diuretic therapy in younger patients who have diabetes has previously been reported to be associated with excess mortality [116]; however, this does not appear to be a problem in the elderly. Tuomilehto and colleagues [117] conducted a subgroup analysis of the Syst-Eur trial participants to assess the benefits of treating elderly patients who had diabetes and isolated systolic hypertension. They found that patients who had diabetes benefited from treatment and that the magnitude of the benefit was greater in patients who had diabetes compared with those who did not (Table 6).

Table 6
Effect of diabetes on outcomes of treatment of high blood pressure [117]

Outcome	Diabetic patients: adjusted relative HR (*P* compared with placebo)	Non-diabetic patients: adjusted relative HR (*P* compared with placebo)	*P* (difference in benefit between diabetic and nondiabetic patients)
Overall mortality	0.45 ($P = .09$)	0.94 ($P = .55$)	.04
Mortality from cardiovascular disorders	0.24 ($P = .01$)	0.87 ($P = .37$)	.02
Cardiovascular events	0.31 ($P = .002$)	0.74 ($P = .02$)	.01
Stroke	0.27 ($P = .02$)	0.62 ($P = .02$)	.13
Cardiac events	0.37 ($P = .06$)	0.79 ($P = .10$)	.12

Data from Tuomilehto J, Rastenyte D, Birkenhager WH, et al. Effects of calcium-channel blocker in older patients with diabetes and systolic hypertension. N Engl J Med 1999;340:680.

Similar trends were seen in patients who had diabetes in the SHEP trial (although benefits for total mortality and stroke did not reach statistical significance) [118] and in the Chinese trial on isolated systolic hypertension in the elderly [119]. Whether target BP less than 130/80 mm Hg (as is suggested in the JNC 7 guidelines for patients who have diabetes) is appropriate for the elderly remains to be determined. Some of the issues in choosing goal BPs are highlighted by Ames [120].

How well is treatment of hypertension tolerated in the elderly?

Side effects

Several large studies have demonstrated that treatment of elderly hypertensive patients can be accomplished with acceptable side-effect profiles and reasonably high compliance rates. The SHEP Pilot Study demonstrated compliance rates in excess of 80% even in patients over age 80 years [121], with no excess symptoms compared with placebo [107], although hypokalemia and hyperuricemia were more common. The European Working Party on High Blood Pressure in the Elderly reported that dry mouth, nasal stuffiness, and diarrhea were more common in treated (triamterene plus hydrochlorthiazide, with methyldopa added if needed to achieve target) patients, with methyldopa further increasing the likelihood of dry mouth and diarrhea. Treated patients were also more likely to develop hypokalemia, glucose intolerance, elevated creatinine and uric acid levels, and symptomatic gout [122,123]. Where possible, treatment regimens should be simplified, with the clinician mindful of the increasing risk of adverse drug reactions with increasing total number of medications ingested. In a study of 30,000 Medicare enrollees, diuretics were among the medications associated with an increased risk of preventable adverse drug events [124].

In a Department of Veterans Affairs Cooperative Study, 30% of patients achieved goal DBP in the placebo group at the end of 1 year, with the highest response rates in older white patients (38% compared with rates of 27% in older blacks and 23% in younger subjects). Discontinuation for exceeding the BP safety limits was twice as common in the placebo group. Discontinuation of study drug due to adverse effects, however, was higher in the placebo group (13%) compared with the active-treatment group (12%) [125].

In a small trial of middle-aged and elderly patients (average age, 68 years) who had systolic hypertension, Hollenberg and colleagues [126] reported that despite comparable lowering of BP with amlodipine and eplerenone, amlodipine was associated with a significant increase in ankle swelling, headache, facial flushing, constipation, and pronounced heart-beat, whereas eplerenone-treated patients had no significant new or worsening symptoms.

After controlling for baseline risk factors and adjustment for SBP as a time-dependent variable, Somes and coworkers [127] reported (SHEP trial) that in the active treatment arm only, a decrease in DBP of 5 mm Hg increased the risk of stroke (RR = 1.14, 95% CI: 1.05–1.22), coronary heart disease (RR = 1.08, 95% CI: 1.00–1.16), and cardiovascular disease (RR = 1.11, 95% CI: 1.05–1.16), with the effect beginning at DBP less than 65 mm Hg. This effect was seen in men and women, across the full spectrum of baseline disease status, and across all age groups (although small numbers of subjects aged >80 years led to a loss of statistical significance in that population).

Sexual dysfunction

Sexual dysfunction was prevalent in hypertensive men in the Treatment of Mild Hypertension Study (TOMHS). Age greater than 60 years and SBP greater than 140 mm Hg were associated with erectile problems at baseline. The study examined the association between five different medications and the presence of sexual dysfunction at 24 months of therapy, and found that chlorthalidone was associated with the highest incidence of erectile dysfunction (15.7% versus 4.9% in placebo). The other agents (amlodipine, acebutolol, doxazosin, and enalapril) had rates comparable to placebo [128].

Cognitive function and mood

Data are insufficient to determine whether aging affects the impact of antihypertensive agents on cognitive functioning. Muldoon and colleagues [129] reviewed the neuropsychologic consequences of antihypertensive medication use. Individual studies have reported adverse effects of certain β-blockers, nifedipine, reserpine, and diuretic therapy. Inconsistent findings between studies and methodologic differences, however, make it difficult to draw clinically meaningful conclusions. In the SHEP trial, active treatment of isolated systolic hypertension had no measured negative effects and, for some measures, a slight positive effect on cognitive, physical, and leisure function. There was no effect on measures related to emotional state [130]. As with any drug in the elderly, a temporal relationship between worsening cognition and the initiation of a new medication should prompt the clinician to evaluate the possibility of drug-induced cognitive dysfunction.

Dyslipidemia and other metabolic disruptions

Monane and coworkers [131] examined the New Jersey Medicaid and Medicare programs and found that elderly (65–99 years old) enrollees who were newly initiated on low-dose thiazide diuretic antihypertensive medications between 1981 and 1989 were not more likely to be subsequently

started on a lipid-lowering agent, although users of high-dose thiazides ($\geq$50 mg) had subsequent lipid-lowering therapy started nearly twice as often. Analysis of the SHEP trial (chlorthalidone first step) data revealed an insignificant increase in the development of new diabetes, although small effects on fasting glucose (+3.6 mg/dL, $P < .01$), total cholesterol (+3.5 mg/dL, $P < .01$), high-density lipoprotein (−0.77 mg/dL), creatinine (+0.03 mg/dL), triglycerides (+17 mg/dL), uric acid (+0.06 mg/dL), and potassium (−0.3 mmol/L) were observed [132].

Diabetes

Concern has been raised about the potential for β-blockers to attenuate the autonomic response, thereby increasing the risk of hypoglycemia. Shorr and colleagues [133] evaluated 13,559 elderly (mean age, 78 ± 7 years) participants in Tennessee's Medicaid program and found that there was no statistically significant increase or decrease in the risk of serious hypoglycemia among users of any class of antihypertensive agents compared with nonusers of antihypertensive drugs.

Accelerated hypertension

There have been multiple reports of adverse events related to precipitous drops in BP in patients with accelerated hypertension or hypertensive emergencies. Barring immediate life-threatening elevations of BP (eg, associated with acute ischemia), attempts should be made to lower BP over hours rather than over minutes, allowing time to reset the cerebral blood flow autoregulatory mechanisms. Because of the high prevalence of systolic hypertension and its attendant risk of cerebrovascular disease, elderly patients might be expected to be at higher risk of precipitous drops in BP. Although any agent that produces such a drop could provoke adverse effects, short-acting nifedipine has been singled out as a known culprit [134] and should be avoided in the elderly.

The very elderly

Although existing data demonstrate the risk associated with high BP and the benefits of treatment in the middle-aged and the "young old" (65–75 years), there is a growing body of data that suggests that it may be inappropriate to extrapolate these results to the very old ($\geq$85 years). Vaitkevicius and coworkers [135] demonstrated that in frail elderly subjects 80 years and older, an aerobic exercise program is associated with a significant decline in resting SBP (146 ± 18 versus 133 ± 14 mm Hg, $P = .01$) and improves VO_2max. The Leiden 85 Plus study (mean age, 90 years), however, looked at all-cause mortality with a 5- to 7-year follow-up. Lower DBPs were associated with higher mortality rates, although most of

this effect of low BP disappeared after controlling for multiple other risk factors [136]. After adjustment for age, sex, and baseline variables of health status, SBP (even >200 mm Hg) was not predictive of all-cause mortality, but DBP re-emerged as a predictor of cardiovascular mortality. In addition, Goodwin [137] pointed out that although the Framingham Heart Study found a positive linear relationship between BP and cardiovascular mortality in younger (35–64 years) and older (65–84 years) populations, when the sample is divided into 10-year increments, the positive association is seen only up to the 65- to 74-year age group. In the 75- to 84-year age group, SBP and DBP become inversely associated with cardiovascular mortality in men and women. In the Established Populations for Epidemiological Studies in the Elderly cohorts, in men, the positive relationship between SBP and survival persisted even after adjusting for age, functional status, medication use, medical diagnoses, and cognitive function. There was no relationship between BP and survival in women 85 years and older [138]. In the European Working Party on High Blood Pressure in the Elderly trial, the benefits of treatment were lost in patients over age 80 years [139,140].

Gueyffier and coworkers [141] conducted a meta-analysis of trials of hypertension in the elderly, limiting their analysis to data in patients over age 80 years. They found that treatment prevented 34% (95% CI: 8–52) of strokes. Although rates of major cardiovascular events and heart failure decreased 22% and 39%, respectively, there was no treatment benefit derived for cardiovascular death and a nonsignificant 6% (95% CI: −5 to 18) excess of death from all causes. Moreover, these investigators pointed out that the treatment benefits observed were not robust. ''The addition of a single hypothetical trial of proper design (ad hoc power) with no treatment effect would be enough to make the results non-significant'' [141].

To address the concerns raised from these studies and from epidemiologic information, the Hypertension in the Very Elderly Trial Working Group initiated a study in patients 80 years and older. Patients were allocated randomly to a diuretic-based regimen, to an ACE inhibitor–based regimen, or to no treatment. The calcium channel blocker diltiazem was added to these regimens as needed to achieve target BP control. Data from the open-design pilot study revealed a nonsignificant increase in mortality for the diuretic-based regimen (HR = 1.31, 95% CI: 0.75–2.27) and the ACE inhibitor–based regimen (HR = 1.14, 95% CI: 0.65–2.02). Fatal and nonfatal strokes were significantly reduced in the diuretic group (HR = 0.31, 95% CI: 0.12–0.79) but only insignificantly in the ACE inhibitor group (HR = −0.69, 95% CI: 0.30–1.31). Insignificant increases in cardiovascular, cardiac, and non–cardiovascular disease mortality were also noted despite (or perhaps because of) the 23/11–mm Hg drop in BPs in the active treatment groups. No significant differences in creatinine, potassium, or uric acid levels occurred in any group [142]. The larger trial has been designed as a randomized, blinded trail and is currently under way [143].

Summary

Hypertension is predictive of a wide variety of subsequent adverse events in elderly patients, at least up to the age of 80 years. Treatment can reduce these adverse outcomes, although the benefits in the very elderly remain somewhat unclear. In the very elderly, there appears to be a reduction in cardiovascular events, but this reduction is perhaps at the expense of an increase in overall mortality. Target BPs in the elderly remain controversial. Among patients who have not had previous stroke or significant cardiovascular or renal disease, the benefits of reducing the SBP below 159 mm Hg are well documented. There is some evidence to suggest, however, that if doing so increases the day–night difference in BP by more than 20% or is associated with a decline in DBP below 65 mm Hg, then the benefits of treatment may be attenuated or lost. In addition, there is some suggestion that reducing SBP consistently below 135 mm Hg may accelerate cognitive decline.

There appears to be a role for sodium restriction in those who can comply without otherwise compromising nutrient intake. Likewise, exercise may be beneficial and have benefits beyond simply lowering BP. Weight loss in those who are overweight may also help in lowering the BP. For most patients, low-dose thiazides such as hydrochlorothiazide are likely to be the appropriate first-line therapy (even in patients who have diabetes) unless they exacerbate or precipitate urinary incontinence or gout or complicate concomitant drug therapy (eg, lithium treatment of bipolar disorder). In very elderly patients, the apparent beneficial effects on strokes, major cardiovascular events, and heart failure rates may justify treating despite lack of benefit on overall mortality.

References

[1] American Heart Association, Learn and Live; Statistical Fact Sheet-Populations; Older Americans and Cardiovascular Disease Statistics. Available at: www.americanheart.org/downloadable/heart/1103832534191FS08OLD5.pdf. Accessed February 24, 2005.

[2] US Census Bureau, Decennial Census and Projections. Older Americans 2004: key indicators of wellbeing. Available at: www.aginstats.gov. Accessed February 24, 2005.

[3] Sohyoun NR, Lentzner H, Hoyeret D, et al. Trends in causes of death among the elderly. Aging Trends. No. 1. Hyatsville (MD): National Center for Health Statistics; 2001. Available at: www.cdc.gov/nchs/data/agingtrends/01death.pdf. Accessed February 24, 2005.

[4] McClellan W, Hall WD, Brogan D, et al. Isolated systolic hypertension: declining prevalence in the elderly. Prev Med 1987;16:686–95.

[5] Chobanian AV, Bakris GL, Balck HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. JAMA 2003;289:2560–72.

[6] Psaty BM, Furgerg CD, Kuller LH, et al. Isolated systolic hypertension and subclinical cardiovascular disease in the elderly. JAMA 1992;268:1287–91.

[7] Auseon A, Ooi WL, Hossain M, et al. Blood pressure behavior in the nursing home: implications for diagnosis and treatment of hypertension. J Am Geriatr Soc 1999;47:285–90.

[8] Sagie A, Larson M, Levy D. The natural history of borderline isolated hypertension. N Engl J Med 1993;329:1912–7.
[9] Hakala SM, Tilvis RS. Determinants and significance of declining blood pressure in old age. Eur Heart J 1998;19:1872–8.
[10] Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population: results from the Third National Health and Nutrition Examination Survey, 1988–1991. Hypertension 1995;25:305–13.
[11] State-specific trends in self-reported blood pressure screening and high blood pressure—United States, 1991–1999. MMWR Morb Mortal Wkly Rep 2002;51(21):456–60.
[12] Egan BM, Lackland DT, Cutler NE. Awareness, knowledge, and attitudes of older Americans about high blood pressure. Arch Intern Med 2003;163:681–7.
[13] Franklin SS, Jacobs MJ, Wong ND, et al. Predominance of isolated systolic hypertension among middle-aged and elderly US hypertensives: analysis based on National Health and Nutrition Examination Survey (NHANES) III. Hypertension 2001;37(3):869–74.
[14] Hyman DK, Pavlik VN. Characteristics of patients with uncontrolled hypertension. N Engl J Med 2001;345(7):479–86.
[15] Gambassi G, Lapane K, Sgadari A, et al. Prevalence, clinical correlates, and treatment of hypertension in elderly nursing home residents. Arch Intern Med 1998;158:2377–85.
[16] Hajjar IM, Grim CE, Kotchen TA. Dietary calcium lowers the age-related rise in blood pressure in the United States: the NHANES III survey. J Clin Hypertens (Greenwich) 2003; 5(2):122–6.
[17] Hajjar IM, Grim CE, George V, et al. Impact of diet on blood pressure and age-related changes in blood pressure in the US population: analysis of NHANES III. Arch Intern Med 2001;161(4):589–93.
[18] Gurwitz JH, Avorn J, Bohn RL, et al. Initiation of antihypertensive treatment during nonsteroidal anti-inflammatory drug therapy. JAMA 1994;272:781–6.
[19] Johnson AG, Nguyed TV, Day RO. Nonsteroidal anit-inflammatory drugs may elevate blood pressure. Ann Intern Med 1994;121:289–300.
[20] Coates ML, Rembold CM, Farr BM. Pseudoephedrine did not increase blood pressure in hypertension. J Fam Pract 1995;40:22–6.
[21] Dinenno FA, Dietz NM, Joyner MJ. Aging and forearm postjunctional alpha-adrenergic vasoconstriction in healthy men. Circulation 2002;106(11):1349–54.
[22] Nash D, Magder L, Lustberg M, et al. Blood lead, blood pressure, and hypertension in perimenopausal and postmenopausal women. JAMA 2003;289:1523–32.
[23] Wilking AVB, Belanger A, Kannel WB, et al. Determinants of isolated systolic hypertension. JAMA 1988;260:3451–5.
[24] Scuteri A, Bos AJG, Brand LJ, et al. Hormone replacement therapy and longitudinal changes in blood pressure and postmenopausal women. Ann Intern Med 2001;135: 229–38.
[25] He J, Ogden LG, Vupputuri S, et al. Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults. JAMA 1999;282:2027–34.
[26] Strazzullo P, Iacone R, Iacoviello L, et al. Genetic variation in the renin-angiotensin system and abdominal adiposity in men: the Olivetti Prospective Heart Study. Ann Intern Med 2003;138:17–23.
[27] Nieto FJ, Herrington DM, Redline S, et al. Sleep apnea and markers of vascular endothelial function in a large community sample of older adults. Am J Respir Crit Care Med 2004; 169(3):354–60.
[28] Ancoli-Israel S, Gehrman P, Kripke DF, et al. Long-term follow-up of sleep disordered breathing in older adults. Sleep Med 2001;2(6):511–6.
[29] Lakatta E. Cardiovascular system. In: Masoro E, editor. Handbook of physiology, section 11. Aging. New York: Oxford University Press; 1995. p. 413–74.
[30] Fleg JL. Alterations in cardiovascular structure and function with advancing age. Am J Cardiol 1986;57:33C–44C.

[31] Vaitkevicius PV, Fleg JL, Engel JH, et al. Effects of age and aerobic capacity on arterial stiffness in healthy adults. Circulation 1993;88:1456–62.
[32] Smulyan S, Safar ME. The diastolic blood pressure in systolic hypertension. Ann Intern Med 2000;132:233–7.
[33] Berry KL, Cameron JD, Dart AM, et al. Large-artery stiffness contributes to the greater prevalence of systolic hypertension in elderly women. J Am Geriatr Soc 2004;52: 368–73.
[34] Pan HYM, Hoffman BB, Pershe RA, et al. Decline in beta adrenergic receptor-mediated vascular relaxation with aging in man. J Pharmacol Exp Ther 1986;239(3):802–7.
[35] Kawamoto A, Shimada K, Matsubayashi K, et al. Cardiovascular regulatory functions in elderly patients with hypertension. Hypertension 1989;13:401–7.
[36] Messerli FG, Glade LB, Dreslinski GR, et al. Hypertension in the elderly: haemodynamic, fluid volume and endocrine findings. Clin Sci 1981;61:393s–4s.
[37] Messerli FG, Sundgaard-Riise K, Ventura HO, et al. Essential hypertension in the elderly: haemodynamics, intravascular volume, plasma renin activity, and circulating catecholamine levels. Lancet 1983;2(8357):983–6.
[38] Sowers JR, Mohanty PK. Effect of advancing age on cardiopulmonary baroreceptor function in hypertensive men. Hypertension 1987;10:274–9.
[39] Mukai S, Gagnon M, Iloputaife I, et al. Effect of systolic blood pressure and carotid stiffness on baroreflex gain in elderly subjects. J Gerontol 2003;58A(7):626–30.
[40] Kannel WB. Some lessons in cardiovascular epidemiology from Framingham. Am J Cardiol 1976;37:269–82.
[41] Sutton KC, Dai WS, Kuller LH. Asymptomatic carotid artery bruits in a population of elderly adults with isolated systolic hypertension. Stroke 1985;16(5):781–4.
[42] Vokonas PS, Kannel WB, Cupples LA. Epidemiology and risk of hypertension in the elderly: the Framingham Study. J Hypertens 1988;6(Suppl 1):S3–9.
[43] Staessen JA, Gasowski J, Wang JG, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. Lancet 2000;355:865–72.
[44] Alli C, Avanzini F, Bettelli G, et al. The long-term prognostic significance of repeated blood pressure measurements in the elderly. Arch Intern Med 1999;159:1205–12.
[45] Mattace-Raso FUS, van der Cammen TJM, van Popele NC, et al. Blood pressure components and cardiovascular events in older adults: the Rotterdam Study. J Am Geriatr Soc 2004;52:1538–42.
[46] Seshadri S, Wolf PA, Beiser A, et al. elevated midlife blood pressure increases stroke risk in elderly persons. Arch Intern Med 2001;161:2343–50.
[47] Haider AW, Larson MG, Franklin SS, et al. Systolic blood pressure, diastolic blood pressure, and pulse pressure as predictors of risk for congestive heart failure in the Framingham Heart Study. Ann Intern Med 2003;138:10–6.
[48] van der Meer IM, Iglesisa del Sol A, Hak AE, et al. Risk factors for progression of atherosclerosis measured at multiple sites in the arterial tree: the Rotterdam Study. Stroke 2003;34:2374–9.
[49] van Leeuwen R, Ikram MK, Vingerling JR, et al. blood pressure, atherosclerosis, and the incidence of age-related maculopathy: the Rotterdam Study. Invest Ophthalmol Vis Sci 2003;44:3771–7.
[50] Kuo HK, Sorond F, Iloputaife I, et al. Effect of blood pressure on cognitive functions in elderly persons. J Gerontol (Med Sci) 2004;59A(11):1191–4.
[51] Wallace RB, Lemke JH, Morris MC, et al. Relationship of free-recall memory to hypertension in the elderly. the Iowa 65+ Rural Health Study. J Chron Dis 1985;38(6): 475–81.
[52] Glynn RK, Beckett LA, Hebert LE. Current and remote blood pressure and cognitive decline. JAMA 1999;281:438–45.
[53] Petitti DB, Crooks VC, Buckwalter JG, et al. Blood pressure levels before dementia. Arch Neurol 2005;62:112–6.

[54] de Leeuw FE, de Groot JC, Oudkerk M, et al. Hypertension and cerebral white matter lesions in a prospective cohort study. Brain 2002;125:765–72.
[55] van Dijk EJ, Breteler MMB, Schmidt R, et al. The association between blood pressure, hypertension, and cerebral white matter lesions: Cardiovascular Determinants of Dementia Study. Hypertension 2004;44:625–30.
[56] Sacktor N, Gray S, Kawas C. Systolic blood pressure within an intermediate range may reduce memory loss in an elderly hypertensive cohort. J Geriatr Psychiatry Neurol 1999;12: 1–6.
[57] 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;265:3255–65.
[58] Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomized double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trail. Lancet 1998;352: 1347–51.
[59] Forette F, Seux ML, Staessen JA, et al. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. Arch Intern Med 2002;162(18):2046–52.
[60] in't Veld BA, Ruitenberg A, Hoffman A, et al. Antihypertensive drugs and incidence of dementia: the Rotterdam Study. Neurobiol Aging 2001;22:407–12.
[61] Drayer JIM, Weber MA, Deyoung JL, et al. Circadian blood pressure patterns in ambulatory hypertensive patients: effects of age. Am J Med 1982;73:493–9.
[62] Pasqualini R, Foroni M, Salvioli G, et al. The ''nondipper'' elderly: a clinical entity or a bias? J Am Geriatr Soc 2004;52:967–71.
[63] Kario K, Matsuo T, Kobayashi H, et al. Nocturnal fall of blood pressure and silent cerebrovascular damage in elderly hypertensive patients. Hypertension 1996;27: 130–5.
[64] Nakamura K, Oita J, Yamaguchi T. Nocturnal blood pressure dip in stroke survivors: a pilot study. Stroke 1995;26:1373–8.
[65] Cavallini MC, Roman MJ, Blank SG, et al. Association of the auscultatory gap with vascular disease in hypertensive patients. Ann Intern Med 1996;124:877–83.
[66] Hla KM, Feussner JR. Screening for pseudohypertension. Arch Intern Med 1988;148: 673–6.
[67] Bailey RH, Bauer JH. A review of common errors in the indirect measurement of blood pressure. Arch Intern Med 1993;153:2741–8.
[68] Hla KM, Vokaty KA, Feussner JR. Observer error in systolic blood pressure measurements in the elderly. Arch Intern Med 1986;146:2373–6.
[69] Bailey RH, Knaus VL, Bauer JH. Aneroid sphygmomanometers: an assessment of accuracy at a university hospital and clinics. Arch Intern Med 1991;151:1409–12.
[70] Smith NL, Psaty BM, Rutan GH, et al. The association between time since last meal and blood pressure in older adults: the cardiovascular health study. J Am Geriatr Soc 2003; 51(6):824–8.
[71] Kohara K, Jiang Y, Igase M, et al. Postprandial hypotension is associated with asymptomatic cerebrovascular damage in essential hypertensive patients. Hypertension 1999;33(1 Pt 2):565–8.
[72] Le Couteur DG, Fisher AA, Davis MW, et al. Postprandial systolic blood pressure responses of older people in residential care: association with risk of falling. Gerontology 2003;49(4):260–4.
[73] Ensrud KE, Nevitt MC, Yunis C, et al. Postural hypotension and postural dizziness in elderly women. The study of osteoporotic fractures. The Study of Osteoporotic Fractures Research Group. Arch Intern Med 1992;152(5):1058–64.
[74] Mukai S, Lipsitz LA. Orthostatic hypotension. Clin Geriatr Med 2002;18(2):253–68.
[75] Hossain M, Ooi WL, Lipsitz LA. Intra-individual postural blood pressure variability and stroke in elderly nursing home residents. J Clin Epidemiol 2001;54(5):488–94.

[76] Luukinen H, Koski K, Laippala P, et al. Orthostatic hypotension and the risk of myocardial infarction in the home-dwelling elderly. J Intern Med 2004;255(4):486–93.
[77] Masuo K, Mikami H, Ogihara T, et al. Changes in frequency of orthostatic hypotension in elderly hypertensive patients under medications. Am J Hypertens 1996;9(3):263–8.
[78] Vogt MT, Cauley JA, Newman A, et al. Decreased ankle/arm blood pressure index and mortality in elderly women. JAMA 1993;270:465–9.
[79] Sutton KC, Wolfson SK, Kuller LH. Carotid and lower extremity arterial disease in elderly adults with isolated systolic hypertension. Stroke 1987;18:817–22.
[80] Tuomilehto J. Body mass index and prognosis in elderly hypertensive patients: a report from the European Working Party on High Blood Pressure in the Elderly. Am J Med 1991; 90(Suppl 3A):34S–41S.
[81] Fagard R. Serum cholesterol levels and survival in elderly hypertensive patients: analysis of data from the European Working Party on High Blood Pressure in the Elderly. Am J Med 1991;90(Suppl 3A):62S–3S.
[82] Wachtell K, Insen H, Olsen MH, et al. Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: the LIFE Study. Ann Intern Med 2003;139: 901–6.
[83] Staessen JA, Thijs L, Fagard R, et al. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. JAMA 1999;282: 539–46.
[84] Wing LMH, Brown MA, Beilin LJ, et al. ''Reverse white-coat hypertension'' in older hypertensives. J Hypertens 2002;20:639–44.
[85] Kannel WB, Sorlie P, Gordon T. Labile hypertension: a faulty concept? Circulation 1980; 61(5):1183–7.
[86] Tsuji I, Imai Y, Nagai K, et al. Proposal of reference values for home blood pressure measurement prognostic criteria based on a prospective observation of the general population in Ohasama, Japan. Am J Hypertens 1997;10(4 pt 1):409–18.
[87] Hozawa A, Ohkubo T, Nagai K, et al. Prognosis of isolated systolic and isolated diastolic hypertension as assessed by self-measurement of blood pressure at home. Arch Intern Med 2000;160:3301–6.
[88] Hitzenberger G, Magometschnigg D. Blood pressure characteristics of hypertensive patients in Austria as determined by self-monitoring (SCREEN-II). Blood Press 2003; 12(3):134–8.
[89] Thijs L, Staessen JA, Celis H, et al. Reference values for self-recorded blood pressure. Arch Intern Med 1998;158:481–8.
[90] Turnbull SM, Magennis SP, Turnbull CJ. Patient self-monitoring of blood pressure in general practice: the 'inverse white-coat' response. Br J Gen Pract 2003;53(488):221–3.
[91] Cuspidi C, Michev I, Meani S, et al. Left ventricular hypertrophy in treated hypertensive patients with good blood pressure control outside the clinic, but poor clinic blood pressure control. J Hypertens 2003;21(8):1575–81.
[92] Thijs L. Age-related hypotensive effect of placebo and active treatment in patients older than 60 years. Am J Med 1991;90(Suppl 3A):24S–6S.
[93] Joossens JV, Kesteloot H. Trends in systolic blood pressure, 24-hour sodium excretion, and stroke mortality in the elderly in Belgium. Am J Med 1991;90(Suppl 3A):5S–11S.
[94] Niarchos AP, Weinstein DL, Laragh JH. Comparison of the effects of diuretic therapy and low sodium intake in isolated systolic hypertension. Am J Med 1984;77:1061–8.
[95] Kaplan NM. Electrolytes: their importance in hypertension in the elderly. Geriatr Cardiovasc Med 1988;1:123–7.
[96] Midgley JP, Mathew AG, Greenwood CM, et al. Effect of reduced dietary sodium on blood pressure. A meta-analysis of randomized controlled trials. JAMA 1986;275:1590–7.
[97] Geleijnse JM, Witteman JC, Bak AA, et al. Reduction in blood pressure with a low sodium, high potassium, high magnesium salt in older subjects with mild to moderate hypertension. BMJ 1994;309(6952):436–40.

[98] Luft FC, Weinberger MH, Fineberg NS, et al. Effects of age on renal sodium homeostasis and its relevance to sodium sensitivity. Am J Med 1987;82(Suppl 1B):9–15.
[99] Hoption Cann SA, van Netten JP, van Netten C. Iodized Salt and hypertension. Arch Intern Med 2002;162:104.
[100] Khaw KT, Barret CE. Dietary potassium and stroke-associated mortality: a 12-year prospective population study. N Engl J Med 1987;316:235–40.
[101] Whelton PK, He J, Cutler JA, et al. Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled trials. JAMA 1997;277:1624–32.
[102] Applegate WB, Miller ST, Elam JT, et al. Nonpharmacologic intervention to reduce blood pressure in older patients with mild hypertension. Arch Intern Med 1992;152:1162–6.
[103] Whelton PK, Appel LJ, Espeland MA, et al. Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized Trial of Nonpharmacologic Interventions in the Elderly (TONE). JAMA 1998;279:839–46.
[104] Pearce LK, Engel BT, Burton JR. Behavioral treatment of isolated systolic hypertension in the elderly. Biofeedback Self Regul 1989;14(3):207–17.
[105] Jajich CL, Ostfeld AM, Freeman DH. Smoking and coronary heart disease mortality in the elderly. JAMA 1984;252:2831–4.
[106] Cushman WC, Khatri I, Materson BJ, et al. Treatment of hypertension in the elderly: III. Response of isolated systolic hypertension to various doses of hydrochlorthiazide—results of a Department of Veterans Affairs Cooperative Study. Arch Intern Med 1991;151: 1954–60.
[107] Hulley SB, Furberg CD, Gurland B, et al. Systolic Hypertension in the Elderly Program (SHEP): antihypertensive efficacy of chlorthalidone. Am J Cardiol 1985;56:913–20.
[108] Perry HM, Davis BR, Price TR, et al. Effect of treating isolated systolic hypertension on the risk of developing various types and subtypes of stroke. JAMA 2000;284:465–71.
[109] Kostis JB, Davis BR, Cutler J, et al. Prevention of heart failure by antihypertensive drug treatment in older persons with systolic hypertension. JAMA 1997;278:212–6.
[110] Bleumink BS, Deinum J, Mosterd A, et al. Antihypertensive treatment is associated with improved left ventricular geometry: the Rotterdam Study. Pharmacoepidemiol Drug Saf 2004;13:703–9.
[111] Schulman ST, Weiss JL, Becker LC, et al. The effects of antihypertensive therapy on left ventricular mass in elderly patients. N Engl J Med 1990;322:1350–6.
[112] Applegate W, Dismuke SE, Runyan JW. Treatment of hypertension in the elderly: a time for caution? J Am Geriatr Soc 1984;32:21–3.
[113] ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. 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 2002;288(23): 2981–97.
[114] Wing LM, Reid CM, Ryan P, et al. A comparison of outcomes with angiotensin-converting enzyme inhibitors and diuretics for hypertension in the elderly. N Engl J Med 2003;348: 583–92.
[115] Pahor M, Shorr RI, Somes GW, et al. Diuretic-based treatment and cardiovascular events in patients with mild renal dysfunction enrolled in the Systolic Hypertension in the Elderly Program. Arch Intern Med 1998;158:1340–5.
[116] Warram JH, Laffel LM, Valsania P, et al. Excess mortality associated with diuretic therapy in diabetes mellitus. Arch Intern Med 1991;151(7):1350–6.
[117] Tuomilehto J, Rastenyte D, Birkenhager WH, et al. Effects of calcium-channel blocker in older patients with diabetes and systolic hypertension. N Engl J Med 1999;340:677–84.
[118] Curb JD, Pressel SL, Cutler JA, et al. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. JAMA 1996;276:1886–92.

[119] Wang JG, Staessen JA, Gong L, et al. Chinese trial on isolated systolic hypertension in the elderly. Arch Intern Med 2000;160:211–20.
[120] Ames R. Goal blood pressure in treating hypertension. Arch Intern Med 2002;162:105–6.
[121] Black DM, Brand RJ, Greenlick M, et al. Compliance to treatment for hypertension in the elderly patients: the SHEP Pilot Study. J Gerontol 1987;42(5):552–7.
[122] Fletcher AE. Adverse treatment effects in the trial of the European Working Party on High Blood Pressure in the Elderly. Am J Med 1999;90(Suppl 3A):42S–4S.
[123] Staessen J. The Determinants and prognostic significance of serum uric acid in elderly patients of the European Working Party on High Blood Pressure in the Elderly Trial. Am J Med 1999;90(Suppl 3A):50S–4S.
[124] Field TS, Gurwitz JH, Harrold LR, et al. Risk factors for adverse drug events among older adults in the ambulatory setting. J Am Geriatr Soc 2004;52:1349–54.
[125] Preston RA, Materson BJ, Reda DJ, et al. Placebo-associated blood pressure response and adverse effects in the treatment in the treatment of hypertension. Arch Intern Med 2000; 160:1449–54.
[126] Hollenberg NK, Williams GH, Anderson R, et al. Symptoms and the distress they cause: comparison of an aldosterone antagonist and a calcium channel blocking agent in patients with systolic hypertension. Arch Intern Med 2003;163:1543–8.
[127] Somes GW, Pahor M, Shorr RI, et al. The role of diastolic blood pressure when treating isolated systolic hypertension. Arch Intern Med 1999;159:2004–9.
[128] Grimm RH, Grandits GA, Prineas RJ, et al. Sexual dysfunction in men was greater with chlorthalidone than with placebo, acebutolol, amlodipine, doxazosin or enalapril. Hypertension 1997;29:8–14.
[129] Muldoon MF, Waldstein SR, Jennings JR. Neuorpsychological consequences of antihypertensive medication use. Exp Aging Res 1995;21:353–68.
[130] Applegate WB, Pressel S, Wittes J, et al. Impact of the treatment of isolated systolic hypertension on behavioral variables. Results from the Systolic Hypertension in the Elderly Program. Arch Intern Med 1994;154(19):2154–60.
[131] Monane M, Gurwitz JH, Bohn RI, et al. The impact of thiazide diuretics on the initiation of lipid-reducing agents in older people: a population-based analysis. J Am Geriatr Soc 1997; 45:71–5.
[132] The Systolic Hypertension in the Elderly Program. Influence on long-term, low-dose, diuretic-based, antihypertensive therapy on glucose, lipid, uric acid, and potassium levels in older men and women with isolated systolic hypertension. Arch Intern Med 1998;158: 741–51.
[133] Shorr RI, Ray WA, Daugherty JR, et al. Antihypertensives and the risk of serious hypoglycemia in older persons using insulin or sulfonylureas. JAMA 1997;278:40–3.
[134] Grossman E, Messerli FH, Grodzicki T, et al. Should a moratorium be placed on sublingual nifedipine capsules given for hypertensive emergencies and pseudoemergencies? JAMA 1996;276:1328–31.
[135] Vaitkevicius PV, Ebersold C, Shah MS, et al. Effects of aerobic exercise training in community-based subjects aged 80 and older: a pilot study. J Am Geriatr Soc 2002;50(12): 2009–13.
[136] Boshuizen HC, Izaks GJ, van Buuren S, et al. Blood pressure and mortality in elderly people aged 85 and older: community based study. 1998;316:1780–4.
[137] Goodwin JS. Embracing complexity: a consideration of hypertension in the very old. J Gerontol 2003;58A(7):653–8.
[138] Satish S, Freeman DH Jr, Ray L, et al. The relationship between blood pressure and mortality in the oldest old. J Am Geriatr Soc 2001;49(4):367–74.
[139] Birkenhager AA, Broxko P, Bulpitt C, et al. Influence of antihypertensive drug treatment on morbidity and mortality in patients over the age of 60 years. European Working Party on High blood Pressure in the Elderly (EWPHE) results: subgroup analysis. J Hypertens Suppl 1986;4(6):S642–7.

[140] Birkenhager AA, Brixko R, Bulpitt C, et al. Efficacy of antihypertensive drug treatment according to age, sex, blood pressure, and previous cardiovascular disease in patients over the age of 60. Lancet 1986;2(8057):589–92.
[141] Gueyffier F, Bulpitt C, Boissel JP, et al. Antihypertensive drugs in very old people: a subgroup meta-analyisis of randomized controlled trials. Lancet 1999;353:793–6.
[142] Bulpitt CJ, Beckett NS, Cooke J, et al. Results of the pilot study for the Hypertension in the Very Elderly Trial. J Hypertens 2003;21:2409–17.
[143] Bulpitt C, Fletcher A, Beckett N, et al. Hypertension in the Very Elderly Trial (HYVET): protocol for the main trial. Drugs Aging 2001;18:151–64.
[144] Hansson L, Hedner T, Lund-Johansen P, et al. Randomised trial of effects of calcium antagonists compared with diuretics and β-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. Lancet 2000;356: 359–65.
[145] Hansson L, Lindhold LH, Ekbom T, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity. The Swedish Trial in Old Patients with Hypertension-2 study. Lancet 1999;354:1751–6.
[146] Lindholm LH, Hansson L, Ekbom T, et al. Comparison of antihypertensive treatments in preventing cardiovascular events in elderly diabetic patients: results from the Swedish Trial in Old Patients with Hypertension-2. STOP Hypertension-2 Study Group. J Hypertens 2000;18(11):1671–5.
[147] Dahlof B, Lindholm LH, Hansson L, et al. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension. (STOP-Hypertension). Lancet 1991;338:1281–5.
[148] MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. BMJ 1992;304:405–12.
[149] Wing LM, Reid CM, Ryan P, et al. Second Australian National Blood Pressure Study (ANBP2). Australian comparative outcome trial of ACE inhibitor- and diuretic-based treatment of hypertension in the elderly. Management Committee on behalf of the High Blood Pressure Research Council of Australia. Clinical & Experimental Hypertension 1997;19(5–6):779–91.