Medicine Grand Rounds
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TREATING THE ELDERLY HYPERTENSIVE: PROMISES AND PERILS

The primary purpose of this presentation is to describe newly published data that, for the first time, document the ability to delay death and perhaps even more importantly, reduce disability in a very large portion of the elderly population, those who have a significantly elevated blood pressure. The need for such therapy was succinctly stated by P. Rabbitt in the May 9, 1992 Lancet in his review of a book *Successful Aging*. Dr. Rabbitt stated: "The demographics of ageing in the 21st century are already notorious but cannot be sufficiently emphasised. By the year 2000, 20% of the population of the EC and North America will be aged over 60....This burden will not be light: people over 65 already require about 43% of the NHS budget. About 18% of an American's lifetime medical expenditure takes place during the last year of his or her life."

Rabbitt notes the appropriateness of Jim Fries' definition of successful aging as "delaying the onset of illness....so as to compress the lifetime experience of morbidity into the shortest possible period." The successful treatment of hypertension will help achieve that goal.

In the following coverage, some distinction will be made between two patterns of hypertension seen in the elderly: combined systolic and diastolic, the carry over of primary (essential) hypertension common to middle age, and isolated systolic hypertension (ISH), the more frequent form in those over age 65. However, since therapy for both forms seems equally successful, most of the coverage will not make a distinction and will apply to both patterns.

Case 1: WB is a 75 year old man who went to an orthopedist after a fall and was found to have a BP = 210/80. At age 60, his BP was 160/90; at age 70, 180/85. He has noted occasional postural dizziness in the morning. On exam, his supine BP = 210/75; after 2 minutes standing BP = 165/70. Evidences of diffuse atherosclerotic vascular disease included diffuse copper-wiring and few visible vessels on funduscopic, bilateral carotid bruits and weak femoral and dorsalis pedis pulses.

Prevalence

This patient demonstrates typical cardiovascular changes with aging, largely reflecting atherosclerosis. Whereas diastolic pressures tend to plateau before age 60 and drop thereafter, systolic pressures rise progressively (Figure 1). Therefore the incidence of isolated systolic hypertension (ISH), defined as systolic $\geq$ 160, diastolic $\leq$ 90, progressively rises with age: In a recent meta-analysis of diverse, industrialized populations, the prevalence of ISH rose from 5% at age 60 to 12.6% at 70 and 23.6% at 80 (Staessen et al, 1990).

These figures are largely based on single sets of blood pressure measurements in an office setting which leads to considerable overestimation (Silagy and McNeil, 1992). When 24 hour ambulatory recordings were obtained on 318 patients with ISH, mean daytime systolic blood pressure was 27 mm Hg lower than that recorded in the clinic, while diastolic pressure was similar (Cox et al, 1991). This difference was similar to that found in other studies of hypertensive patients including

another of patients with ISH (Figure 2). Cox et al found that ambulatory readings predicted the presence of left ventricular hypertrophy better than did clinic readings, suggesting that the ambulatory readings are more indicative of the usual, long-term level of blood pressure.

Although premature mortality removes a significant number of those with diastolic hypertension before they reach age 65, about 40% of those over age 65 with hypertension in the Framingham study population had diastolic hypertension as well (Vokonas et al, 1988).

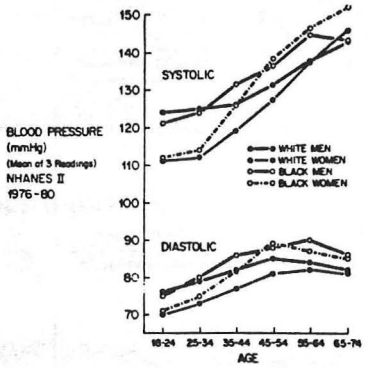

Figure 1: The mean systolic and diastolic blood pressures for white and black men and women in various age groups in the 1976 to 80 National Health and Nutrition Examination Survey. (From Rowland M, Roberts J: NCHS Advance Data, No. 84, Vital and Health Statistics of the National Center for Health Statistics, October 8, 1982)

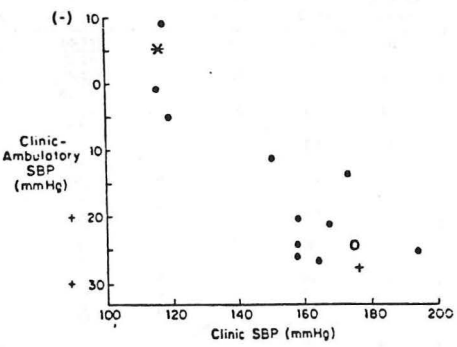

Figure 2: Differences between clinic and daytime ambulatory systolic blood pressure (SBP) at various average levels of clinic SBP from nine published studies; + and O symbols are of isolated systolic hypertensive patients. (From Cox et al, 1991)

Pseudohypertension

Beyond the problems of variability, the elderly may have artifactually elevated pressures by usual indirect cuff measurements because of medial calcification of the large arteries which precludes compression and collapse of the brachial artery despite much higher pressure in the balloon than is present within the artery, i.e., pseudohypertension (Oster and Materson, 1992).

Pseudohypertension should be suspected when the cuff pressure is much higher than the evidence of end organ damage (funduscopic, cardiac, renal) suggests in elderly patients with poorly audible Korotkoff sounds and hard, calcified radial arteries with diminished pulses that are still palpable when the cuff pressure has exceeded the systolic level - Osler's maneuver. This maneuver has not proved to be very useful clinically. If pseudohypertension is suspected, with or without a positive Osler's maneuver, use of an electronic oscillometric device (Infrasonde or Dinamap) will likely provide readings much closer to intra-arterial levels. If still suspected, an intra-arterial measurement is appropriate, certainly preferable to the potential danger of treating pseudohypertension and inducing serious tissue hypoperfusion.

The Risks of ISH

At all ages, systolic pressures are better predictors of cardiovascular risk than are diastolic pressures. Those with ISH have more coronary disease and strokes with an approximate 1% increase in all-cause mortality for each millimeter rise in systolic pressure (Silagy and McNeil, 1992). Data from multiple populations are remarkably consistent: ISH is associated with increased mortality (Table 1).

TABLE 1 Mortality Ratios for Elevated Systolic Blood Pressure Compared with Normotensive Subjects—Data from Prospective Studies

Study	Follow-Up (yrs)	No. of Subjects	Definitions: ISH BP (mm Hg)	Definitions: Normotensive BP (mm Hg)	Mortality Ratios: All Cause	Mortality Ratios: Total Cardiovasc.	Mortality Ratios: Stroke	Mortality Ratios: Myocardial Infarct
Multiple Risk Factor Intervention Trial	6	317,871	>160 / <90	110–119 / 75–79	2.6	NC	NC	NC
			>160 / 80–84	110–119 / 80–84	2.4	NC	NC	NC
Hypertension Detection and Follow-Up Program	8	2,376	>160 / <90	<160 / <90	2.3	NC	NC	NC
Rancho Bernado	6 4	2,636	>160 / <90	<160 / <90	1.5	1.3	2.2	0.6*
Leisure World	6	3,245	>160 / <90	<160 / <90	1.6	6.9	3.0	2.2
Chicago Stroke Study	3	2,772	>180 / <95	<180 / <95	1.6	2.0	2.5	1.7
Chicago Peoples Gas Company	15	976	>140 / <90	<140 / <90	1.7	1.9	NC	2.0
Framingham Study	30	2,470	>160 / <95	<140 / <95	1.9† / 1.9‡	2.1† / 3.1‡	NC / NC	NC / NC
Dutch Civil Servants	15	2,063	>160 / <90	<135 / <90	2.4† / 3.7‡	NC	NC	NC
	25		>160 / <90	<135 / <90	3.2† / 1.7‡	NC	NC	NC

*Among patients not taking medication
†Men
‡Women
BP = blood pressure; Cardiovasc. = cardiovascular mortality; ISH = isolated systolic hypertension; NC = not calculated

A possible exception to the progressive risks of every increment in systolic pressure has been claimed for the very old, i.e., people over 85 years of age. The lesser 5 year mortality in those with systolics from 160 to over 200 compared to those with systolics below 140, however, was almost certainly related to the inclusion of patients with preexisting debilitating cardiac and other diseases that are likely responsible for the lower pressures and higher mortality (Mattila et al, 1988). In a 3 year follow-up of 724 non-institutionalized 84 to 88 year old people in Finland, the lowest mortality rates were noted in those with systolic blood pressure in the range of 140 to 169 and diastolic blood pressure in the range of 70-99 (Heikinheima et al, 1990).

Pathophysiology

The progressive rise in systolic pressures with age is not seen in primitive groups who do not follow our diet and lifestyle (Intersalt 1988). As noted in Framingham, ISH is associated with increasing age, female gender, increased weight in women, and higher levels of systolic and diastolic blood pressure, but not to serum cholesterol, cigarette smoking, glucose intolerance, hematocrit and uric acid (Wilking et al, 1988).

The basic mechanism is the loss of distensibility and elasticity in the large capacitance arteries, a process that was nicely demonstrated over 50 years ago (Hallock and Benson, 1937) (Figure 3).

Hemodynamically, ISH is characterized by a decreased compliance of the large arteries, high peripheral resistance, abnormal diastolic filling but well preserved to increased systolic function with increased left ventricular mass (Pearson et al, 1991). Cardiac output and blood volume may be diminished. Along with the LVH, high levels of ventricular ectopy are found about twice more frequently than in normotensive elderly (Kostis et al, 1992).

Compared to younger hypertensives, elderly patients with combined systolic and diastolic hypertension tend to have lower cardiac output, intravascular volume, renal blood flow and plasma renin activity and higher peripheral vascular resistance, left ventricular wall thickness and mass (Messerli et al, 1983). Some elderly hypertensive patients develop such marked left ventricular hypertrophy as to prevent adequate diastolic filling, i.e., hypertensive hypertrophic cardiomyopathy (Topol et al, 1985; Pearson et al, 1988). The clinical presentation is usually long standing hypertension in elderly black women who have chest pain or become acutely dyspneic on exertion. If not recognized (best by echocardiography demonstrating marked LVH and very high systolic ejection fraction) but incorrectly treated as congestive heart failure with diuretics and vasodilators to unload the left ventricle, the syndrome worsens and may be lethal. Treatment should be with calcium blockers and beta-blockers to slow and improve diastolic filling and function. Pearson et al (1982) also found diuretics and nitrates to sometimes be helpful.

If an abrupt rise in both systolic and diastolic pressure is noted in an elderly patient, atherosclerotic renovascular disease should be suspected. Less commonly, showers of cholesterol emboli into the kidneys from an aortic aneurysm (usually after arteriography) give rise to hypertension (Preston and Materson, 1992).

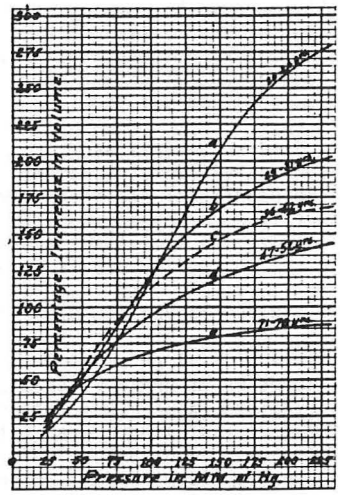

Figure 3: These curves show the relation of percentage increase in volume to increase in pressure for five different age groups and were constructed from the mean values obtained from a number of aortas excised at autopsy. (From Hallock and Benson, 1937)

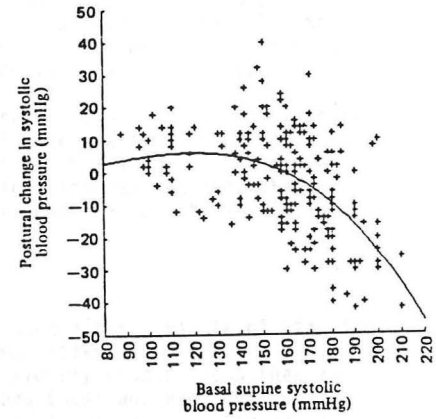

Figure 4: Relationship between basal supine systolic blood pressure and postural change in systolic blood pressure for aggregate data from old subjects. (From Lipsitz et al, 1985)

If baroreceptors were intact, the high systolic pressures resulting from a normal cardiac output entering a nonelastic aorta would be modulated downward. However, the baroreceptor reflex becomes progressively less active with age so that the high systolic pressures persist but, at the same time the fall in pressure that accompanies standing is not immediately countered, thereby leading to increasing postural hypotension with higher levels of basal supine systolic hypertension (Lipsitz et al, 1985) (Figure 4). As in Case 1, the immediate need in many patients with systolic *hypertension* may be to treat their postural *hypotension*. Only then may it be possible to address the hypertension.

Table 2: Age Related Changes Leading to Postural Hypotension

1. Decreased baroreceptor responsiveness
2. Increased stiffness of heart and large arteries
3. Reduced cardiac output
4. Defective cerebral autoregulation
5. Venous pooling
6. Autonomic dysfunction
7. Postprandial hypotension
8. Reduced renin-angiotensin reactivity
9. Systolic hypertension

Cardiovascular Changes with Aging

Normal aging is associated with various changes that may lead to postural hypotension (Table 2). The cardiac output falls with age and, in the elderly with hypertension, it is even lower. When elderly subjects are put under passive postural stress (60°upright tilt), their stroke volume and cardiac index fall further because of an inability to reduce end-systolic volume (Shannon et al, 1991). Blood pressure is maintained through an increase in peripheral resistance. These "normal" changes obviously predispose the elderly to postural hypotension from any process that further reduces fluid volume or vascular integrity.

In particular, as systolic blood pressure rises from atherosclerosis, baroreceptor sensitivity and vascular compliance are further reduced, increasing the likelihood of postural hypotension (Figure 4). Moreover, chronic hypertension shifts the threshold for cerebral autoregulation so that a small fall in systemic blood pressure may precipitate a fall in cerebral blood flow.

The Epidemiology of Postural Hypotension

A 20 mm Hg fall in systolic blood pressure after 1 minute of standing is usually taken as an abnormal response indicative of postural hypotension. Among healthy, normotensive, elderly people, less than 7% will have such a fall (Lipsitz, 1989). Among those who are seen as medical outpatients, about 20% over 65 years of age and 30% over 75 will do so. Among institutionalized elderly, debility from falls caused by postural hypotension is a frequent problem (Jonsson et al, 1990). Common daily activities, in particular eating or minimal exertion, may lead to marked falls in blood pressure. The prevalence of postural hypotension in patients with isolated systolic hypertension was ascertained among the 4736 men and women over age 60 enrolled in the Systolic Hypertension in

the Elderly Program (SHEP) (Applegate et al, 1991). In this generally healthy population who had no limitation of daily activities, postural hypotension was found in 10.4% at 1 minute after arising from a seated position and in 12.0% at 3 minutes with 17.3% having hypotension at one or both time intervals. The prevalence would likely have been higher if the patients had been tested after rising from a supine position.

In elderly people, the postprandial fall in blood pressure may be profound. The maximal fall occurs around 60 minutes and has been shown to relate to a failure of sympathetic nervous system activity as reflected in an absence of a rise in plasma norepinephrine levels (Haigh et al, 1991). The fall in pressure is intensified by a high carbohydrate intake and the subsequent rise in plasma insulin levels could play some role (Potter et al, 1989).

Evaluation

The blood pressure and pulse should be measured carefully with avoidance or at least awareness of recent medications or food intake. A set of readings should be taken after the patient has been lying down for 5 minutes and then immediately and after at least 2 minutes of standing. If the patient is unable to stand, support for stability may be provided but the patient should bear his weight.

Heart rate changes should be noted. If the rate increases less than 10 beats/min despite a postural fall in blood pressure, baroreceptor reflex impairment is likely. Tachycardia above 100 beats/min suggests volume depletion or progressive autonomic failure with postsynaptic denervation supersensitivity (Weiling et al, 1991).

The exam should note pupillary size and responsiveness, abnormal sweating, CNS and peripheral nerve reflexes. Autonomic function can best be tested by the heart rate response to deep breathing and the Valsalva maneuver measured with an electrocardiogram. Most healthy elderly persons have a ratio of the longest R-R interval during expiration to the shortest R-R interval during inspiration that is greater than 1.15.

Two papers in the May 1992 Archives of Internal Medicine present somewhat contradictory evidence about the recognition and meaning of postural hypotension. In one, Streeten and Anderson (1992) describe 7 patients with lightheadedness, fatigue and occasional syncope who had postural hypotension only after 13 to 30 minutes of standing. All but one were relieved by either fludrocortisone or octreotide which also reduced their chronic fatigue. These 7 patients were identified during the same time that 36 patients were seen with postural hypotension that appeared within 3 minutes of standing.

On the other hand, postural *dizziness* was found to be even more common than (19% versus 14%) and often unrelated to postural *hypotension* in 9704 nonblack, ambulatory women aged 65 years and older (Ensrud et al, 1992). The relationship may have been obscured by the too-short period of only one minute of standing that was used to identify postural hypotension. Nonetheless, the observation points to the need to look for postural dizziness in the elderly since it was more strongly associated with history of falling, syncope and impaired functional status than was postural hypotension.

Management

1. Correct precipitating factors and withdraw offending drugs (diuretics, vasodilators, tranquilizers and sedatives)
2. Physical measures
   a. Raise the head of the bed by 15-20°
   b. Arise slowly, in stages, from supine to seated to standing
   c. Dorsiflexion of the feet, handgrip isometric or mental exercise before standing (Goldstein and Shapiro, 1990). Leg-crossing and squatting may help those with autonomic failure (van Lieshout et al, 1992).
   d. Small meals and coffee only in the early morning
   e. Jobst stockings and pressure suits (usually not acceptable)
3. Drugs (Ahmad and Watson, 1990)
   a. Fludrocortisone ± NSAID
   b. For "pure" autonomic dysfunction, pindolol
   c. For CNS dysfunction, desmopressin
   d. If the above fail: ergotamine, yohimbine, alpha-sympathomimetics, dopamine antagonists
   e. The somatostatin analogue, octreotide, has been helpful in patients with autonomic neuropathy, presumably by increasing splanchnic vascular resistance and preventing pooling of blood in the gut after eating (Hoeldtke and Davis, 1991).

TREATMENT OF HYPERTENSION IN THE ELDERLY

As will be noted, we now have strong evidence for the effectiveness of antihypertensive drug therapy in protecting elderly hypertensives from cardiovascular morbidity and mortality, stronger evidence than in the younger hypertensive population. However, before rushing toward drug therapy, the multiple benefits of nondrug therapies - now referred to as lifestyle modifications (Table 3) - need to be reaffirmed. They should be enthusiastically provided and vigorously pursued, preferably before and hopefully instead of drug therapy. Strong confirmation of the value of weight reduction and sodium restriction is provided in the Trials of Hypertension Prevention, Phase 1 (1992).

Although the rigid large arteries that are responsible for the high systolic pressures in the elderly might not be expected to respond to these maneuvers, the fact that they do respond as well or better to the same antihypertensive agents as do the more compliant arteries in the nonelderly with combined systolic-diastolic hypertension can be taken as presumptive evidence that they will also respond to the various nondrug therapies. Fewer trials on these lifestyle modifications have been done on the elderly but enough data are available to document their efficacy.

Table 3: Lifestyle Modifications for Treatment of Hypertension

Stop smoking (mainly for overall cardiovascular health)
Proven value
Lose weight, particularly for upper body obesity
Reduce sodium intake to 110 mmol/d (2.4 g sodium or 6 g of NaCl)
Moderate alcohol intake to no more than 2 usual portions per day
Exercise (isotonic) regularly
Increase potassium intake from fresh fruits and vegetables
Unproven value
Relax and relieve stress
Eat less saturated fat, more fish oils
Maintain adequate calcium and magnesium intake

Smoking Cessation

The role of smoking as a major killer, responsible for over 435,000 deaths, one of every five, in the United States is well known (Fiore, 1992). Of these deaths, cardiovascular causes are about equal to cancer. The role of smoking in aggravating hypertension has been underestimated for a simple reason: Most blood pressure measurements are taken after the patient has not smoked for an hour or longer, waiting in the physician's office or clinic. When ambulatory monitors have taken readings throughout the day while the smoker puffs away, repeated rises in pressure are noted with no tolerance observed and the overall pressure level is definitely higher than in nonsmokers (DeCesaris et al, 1991).

Most physicians do not even ask their patients if they smoke and even fewer give them help in quitting (Frank et al, 1991). We must become aggressive proponents of smoking cessation, even more so with hypertensives regardless of the age of the patient. Major benefits accrue even to the elderly who quit (Samet, 1992). Physicians can be effective agents for smoking cessation, using the simple "Four A's" from the National Cancer Institute (Manley et al, 1992) (Table 4). Under "Assist," the prescription of one of the multiple brands of nicotine patches will likely become common practice, since they have been shown to at least double the quit-rate in people who want to quit and who are given additional psychological support and to cause few systemic side effects such as a rise in blood pressure.

Table 4: Synopsis for Physicians: How to Help Your Patients Stop Smoking

Ask about smoking at every opportunity.
- a. "Do you smoke?"
- b. "How much?"
- c. "How soon after waking do you have your first cigarette?"
- d. "Are you interested in stopping smoking?"
- e. "Have you ever tried to stop before?" If so, "What happened?"

Advise all smokers to stop.
- a. State your advice clearly, for example: "As your physician, I must advise you to stop smoking now."
- b. Personalize the message to quit. Refer to the patient's clinical condition, smoking history, family history, personal interests, or social roles.

Assist the patient in stopping.
- a. Set a quit date. Help the patient pick a date within the next 4 weeks, acknowledging that no time is ideal.
- b. Provide self-help materials. The smoking cessation coordinator or support staff member can review the materials with the patient if desired (call 1-800-4CANCER for NCI's *Quit for Good* materials).
- c. Consider prescribing nicotine gum, especially for highly addicted patients (those who smoke one pack a day or more or who smoke their first cigarette within 30 minutes of waking).
- d. Consider signing a stop-smoking contract with the patient.
- e. If the patient is not willing to quit now:
  Provide motivating literature (call 1-800-4CANCER for NCI's *Why Do You Smoke?* pamphlet).
  Ask again at the next visit.

Arrange follow-up visits.
- a. Set a follow-up visit within 1 to 2 weeks after the quit date.
- b. Have a member of the office staff call or write the patient within 7 days after the initial visit, reinforcing the decision to stop and reminding the patient of the quit date.
- c. At the first follow-up visit, ask about the patient's smoking status to provide support and help prevent relapse. Relapse is common; if it happens, encourage the patient to try again immediately.
- d. Set a second follow-up visit in 1 to 2 months. For patients who have relapsed, discuss the circumstances of the relapse and other special concerns.

From Glynn T, Manley M. How to Help Your Patients Stop Smoking. A National Cancer Institute Manual for Physicians. Bethesda, MD, National Institutes of Health, 1989.

Beyond helping individual patients, health professionals should take a more aggressive role in keeping children from starting to smoke. To help kill off Old Joe the Camel, and other enticements to children's exposure to cigarettes - join Action on Smoking and Health (ASH, 2013 H Street N.W., Washington DC 20006) and Doctors Ought to Care (DOC, 5510 Greenbriar, Suite 235, Houston, Texas 77005).

Weight Reduction

Even small amounts of weight loss in obese hypertensives can lead to significant reductions in blood pressure (Schotte and Stunkard, 1990). The antihypertensive effect may involve the improved sensitivity to insulin that accompanies weight loss (Franssila-Kallunki et al, 1992).

Since smokers who quit usually gain weight (and may go through major psychological dysfunctions) the short-term use of the antidepressant fluoxetine has been advocated at the time of smoking cessation since it usually also causes weight loss (Pomerleau et al, 1991).

Sodium Restriction

The pressor effect of sodium excess and the antihypertensive efficacy of sodium restriction progressively increase with age (Weinberger and Fineberg, 1991; Law et al, 1991). Therefore, moderate sodium restriction (to 100-120 mmol/day) should be advised for all elderly hypertensives. However, they may have at least two additional hurdles to overcome in achieving this goal: First, their taste sensitivity may be less so they may ingest more sodium to compensate; second, they may depend more upon processed, prepackaged foods which are high in sodium rather than being able to get fresh foods that are low in sodium.

Moderation of Alcohol

Excessive alcohol consumption serves as a pressor mechanism, responsible for 5 to 10% of the hypertension found among men (MacMahon, 1987). This almost certainly applies to the elderly who often are alcohol abusers (Hurt et al, 1988). In MacMahon's review, about half of all published data were found to show the pressor effect only when average daily consumption is greater than 2 drinks, the equivalent of one ounce of ethanol. Some even show a lower pressure among these who consumed one or two drinks per day compared to those who drink more (Sharper et al, 1988). The U-shaped pattern of blood pressure noted by Shaper et al closely fits with the pattern of cardiovascular morbidity and mortality related to alcohol consumption in multiple populations (Marmot and Brunner, 1991) (Figure 5). In all but one study out of twenty, those who drank small amounts of alcohol had fewer coronary events than did those who drank none at all. The mechanism almost certainly involves the alcohol-induced rise in HDL cholesterol (Langer et al, 1992).

The best approach is to restrict alcohol consumption to no more than two usual-sized portions per day but there is no need to advise abstinence unless there are overriding religious or health reasons, e.g., a former alcoholic. Such moderation of alcohol consumption will likely prevent a considerable amount of hypertension while, at the same time, provide the protection from coronary disease that comes from moderate drinking.

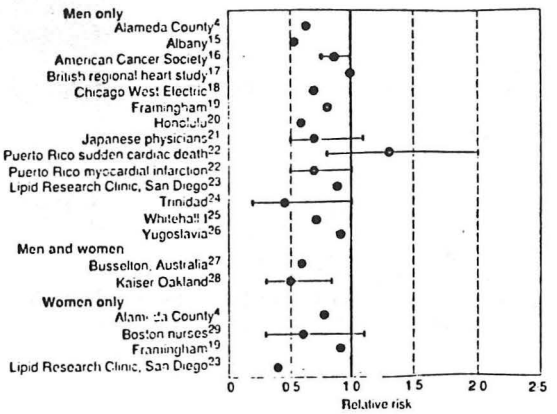

Figure 5: Relative risk of coronary heart disease in moderate drinkers compared with non-drinkers in prospective studies. Bars show 95% confidence interval where available. (Moderate drinking = ≤ 5 units of alcohol daily.) (From Marmot and Brunner, 1991)

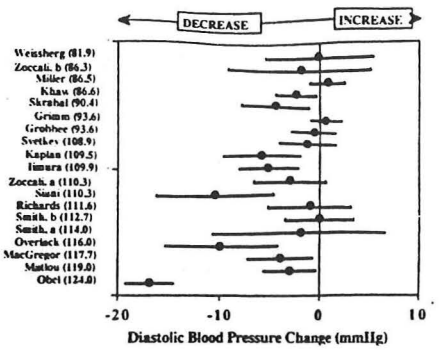

Figure 6: Mean and 95% confidence intervals of the differences in supine diastolic blood pressure after oral potassium supplementation in 19 clinical trials in 586 subjects, 412 hypertensive. Values in parentheses represent the average mean blood pressure during control or placebo. (From Cappuccio and MacGregor, 1991)

Physical Activity

Regular aerobic or dynamic physical activity will lower the blood pressure in most but not all hypertensives including the elderly. Elderly women who perform more physical activity tend to have lower blood pressures, a benefit that is independent of changes in body weight and plasma insulin (Reaven et al, 1991). Moreover, long-term follow-up of people who maintain higher levels of physical activity and achieve higher degrees of physical fitness demonstrates that they have less all-cause mortality (Blair, 1991).

The manner by which repetitive aerobic exercise lowers blood pressure likely involves a dampening of sympathetic nervous system activity. More acutely, the blood pressure tends to remain lower for at least the next 12 hours after low to medium level exercise, reflecting persistent post-exercise vasodilation (Pescatello et al, 1991).

In those who are taking antihypertensive medications, problems may be noted either with the ability to perform exercise or with the ability to reach a training effect. Thus, diuretic-induced hypokalemia may reduce muscle blood flow and beta-blockers may reduce performance by limiting the needed rise in cardiac output (Vanhees et al, 1991). Nonetheless, the hemodynamic responses to exercise can break through beta-blockade and a training effect can be achieved.

Increased Potassium Intake

Although most studies of normotensive people have shown no significant effect of potassium supplementation (Trials of Prevention, 1992), most trials in hypertensive patients have found some lowering of elevated blood pressure (Cappaccio and MacGregor, 1991) (Figure 6).

Moreover, those who eat more potassium-rich natural foods may be protected from stroke (Khaw and Barrett-Connor, 1987) and may achieve better control of hypertension with considerably less antihypertensive medication (Siani et al, 1991).

Despite these generally favorable findings, the routine use of potassium supplements is too costly and potentially hazardous and they should be reserved for those who need potassium repletion. However, the increased consumption of potassium-rich natural foods, as used by Sinai et al (1991), should cost no more and may provide major benefits for those with or without overt hypertension.

Calcium Supplements

Studies of calcium supplements to lower blood pressure have mostly shown little if any effect overall, although a few patients do respond. In a review of all published data, a small but statistically significant 1.8 mm Hg effect on systolic and no effect on diastolic pressures were noted (Cutler and Brittain, 1990). From a study of 103 elderly hypertensives, the authors conclude "There is no evidence for general use of calcium supplementation to reduce blood pressure in an older population (Morris and McCarron, 1992).

Stress Management

Although stress-induced activation of the sympathetic nervous system is likely involved in the pathogenesis of hypertension, it has not been possible to show that relief of stress as provided by various relaxation methods will prevent hypertension, much less provide more than a placebo effect in lowering the pressure in those with established hypertension (Kaufmann et al, 1988).

The Stress of Awakening. These largely negative results of intervention trials do not negate a causal role for stress and may merely mean that the techniques used to relieve stress are inadequate or that it takes much longer to effect a change in the responsiveness to stress.

Sympathetic arousal almost certainly plays a role in the increased occurrence of cardiovascular catastrophes in the early morning hours after awakening from sleep. As nicely shown by Panza et al (1991) in their study of 12 normal subjects, significantly higher levels of basal forearm vascular resistance and lower forearm blood flow are present at 7 AM than at 2 PM or 9 PM. These higher levels of resistance at 7 AM were blunted by the alpha-blocker phentolamine which had lesser effects at 2 PM and 9 PM thereby wiping out the circadian variation in vascular resistance. The nonspecific vasodilator nitroprusside had similar effects at all 3 times of day, preserving the circadian variation but at a uniformly lower level.

Since there is no way to delete the normal endogenous circadian rhythms nor to delay arising from sleep by more than a bit, the sympathetic activation of the early morning hours looms as a significant contributor to an increased risk of cardiovascular diseases at this time. To help prevent these consequences, at least in those who are hypertensive, it seems prudent to monitor the pressure at this time and to use antihypertensive agents that maintain effectiveness during the latter part of the night and early morning hours and which block sympathetic

activity. Both long-acting alpha-blockers and beta-blockers may serve to soften this susceptibility. In addition, a slow gradual rising from supine to upright rather than a sudden jump out of bed may be a safer way to face the coming day, particularly in the elderly who are susceptible to postural hypotension that is almost always worse after sleep.

Fish Oils and Fat

Despite enthusiasm for changes in the amount and nature of dietary fat, these have not been found to have much if any effect on blood pressure (Sachs, 1989).

The omega-3 polyunsaturated fatty acids found in highest concentration in cold water fish are being widely used for various cardiovascular benefits, including a putative antihypertensive effect. Large doses (15 g per day) were shown to induce a 6.5/4.4 mm Hg fall in blood pressure in eight men with mild hypertension (Knapp and FitzGerald, 1989). Elderly subjects obtain similar falls in pressure with 9 g of fish oil per day (Margolin et al, 1991) and, if used in concert with a lower-sodium diet, even as little as 6 g a day (Cobiac et al, 1992).

Coffee and Caffeine

Although caffeine is a mild sympathomimetic, tolerance develops quickly so that little if any effect on blood pressure has been seen over fairly large ranges of consumption of caffeinated beverages. The manner by which coffee is brewed may, however, make a difference: 6 cups a day of boiled coffee (Scandinavian-style) significantly raised the blood pressure in 64 men and women during a 79 day controlled study but 6 cups a day of filtered coffee did not (van Dusseldorp et al, 1991).

On the other hand, the sympathomimetic boost of the caffeine in 2 strong cups of coffee may blunt the early morning postural hypotension in the elderly. To prevent tolerance, no more caffeine should be consumed over the rest of the day.

DRUG TREATMENT

Until recently, little data were available about the effectiveness of antihypertensive therapy in the elderly and the reasonable doubt expressed by most experts about the value of such therapy led many practitioners to hold back. Absent data on the value of therapy, the literature provided many reasons for caution.

Reasons for Current Reticence

1. Reports of increased rates of sudden death (Kannel et al, 1988) and of total mortality (Clausen and Jensen, 1992) among hypertensives receiving antihypertensive medications. Such apparent adversity could, however, reflect preferential selection of high-risk patients for therapy.

2. Multiple reports of iatrogenic illnesses precipitated by antihypertensive and other drug use in the elderly:

   - Inappropriate antihypertensive therapy in the elderly (Jackson et al. Lancet 1976;2:1317-18)
   - Contribution of inappropriate treatment for hypertension to pathogenesis of stroke in the elderly (Jansen et al. Br Med J 1986;293:914-17)
   - Cerebral ischemia and stroke as side effects of antihypertensive treatment; special danger in the elderly (Jansen et al. Neth J Med 1987;30:193-201)
   - Need we poison the elderly so often (Editorial. Lancet 1988;2:20-1)
   - Overtreatment of hypertension in the elderly? (Lernfelt et al. J Hypertension 1990;8:483-90)
   - The role of medication noncompliance and adverse drug reactions in hospitalizations of the elderly (Col et al. Arch Intern Med 1990;150:841-45)

   This last paper reviewed 315 consecutive admissions of patients over age 65 to the medical service of an acute care hospital between June and August 1987. Of this number, 28.2% of the admissions were drug-related, 16.8% from adverse reactions, 11.4% from noncompliance. At the same time the widespread and often promiscuous prescribing of drugs to the elderly has been well documented: In the series by Col et al, 43% were taking 4 or more prescription medications; in a survey among English elderly quoted in the Lancet editorial, almost 40% of those over 80 were on a diuretic; in Florida, the average number of drugs taken by ambulatory elderly subjects rose from 2.9 in 1978-79 to 4.1 in 1987-88 (Stewart et al, 1991).

3. Increasing awareness that the elderly often have many features predisposing them to additional risks from antihypertensive therapy (Table 5). Although the generally believed relation between advancing age and the risks from adverse drug reactions cannot be documented (Gurwitz and Avorn, 1991), there are multiple factors that could add risks to the elderly (Beers and Ouslander, 1989).

Table 5: Factors That Might Contribute to Increased Risk of Pharmacological Treatment of Hypertension in the Elderly

Factors	Potential Complications
Diminished Baroreceptor Activity	Orthostatic Hypotension
Impaired Cerebral Autoregulation	Cerebral Ischemia with Small Falls in Systemic Pressure
Decreased Intravascular Volume	Orthostatic Hypotension Volume Deficiency Hyponatremia
Sensitivity to Hypokalemia	Arrhythmia, Muscular Weakness
Decreased Renal and Hepatic Function	Drug Accumulation
Polypharmacy	Drug Interaction
CNS Changes	Depression, Confusion

4. The possibility of a J-curve, wherein the incidence of coronary disease falls progressively as diastolic blood pressure is reduced to around 85 mm Hg only to go back up at lower pressures (Farnett et al, 1991) has caused many to be concerned that the elderly might be particularly susceptible since so many have naturally lower diastolic pressure. Among the Framingham study cohort, no such J curve was found among low risk subjects without a prior myocardial infarction, but it was seen in elderly patients who had survived an MI (D'Agostino et al, 1991). In the SHEP study, no J curve for CHD was seen, as reported at the American Society of Hypertension meeting on May 8, 1992.

5. Increasing recognition of the frequency and dangers of postural (Shannon et al, 1986) and postprandial (Lipsitz et al, 1983; Peitzman and Berger, 1989) hypotension in the elderly with the awareness that the use of antihypertensive medication could worsen the problem.

6. Concerns that antihypertensive medications could further impair the already vulnerable cognitive functions of the hypertensive elderly. Such concerns were valid in the old days when reserpine and aldomet were widely used. With current therapies (diuretics, beta-blockers, etc), no significant loss of cognitive function has been seen in carefully conducted studies (Goldstein, 1992; Goldstein et al, 1990). Lingering doubts about the depressive effects of beta-blockers seem to have been dispelled (Prisant et al, 1991).

7. Recognition of hypertensive hypertrophic cardiomyopathy in the elderly, wherein symptoms of dyspnea or chest pain are due to severe concentric cardiac hypertrophy, leaving only a small left ventricular cavity and supernormal indices of systolic function (Topol et al, 1985; Pearson et al, 1988). Such patients given vasodilator and diuretic therapies to "unload" the heart (presumed to be in congestive failure with decreased systolic ejection) have suffered severe hypotensive reactions.

Reasons for Future Enthusiasm

The past and current reticence, grounded in appropriate concerns, will almost certainly give way to a major increase in the recognition and active drug therapy of elderly hypertensives. We wrote in mid-1990: "Most physicians have been reluctant to treat elderly hypertensive subjects because elevated blood pressure in this age group was accepted as a 'normal' change with aging.....Antihypertensive therapy was thought to result in more harm than good. Thus, a systolic blood pressure of '100 plus age' was acceptable in the elderly" (Tjoa and Kaplan, 1990). In late 1991, an editorialist in the Lancet commented on the implications of two new trials of treatment of hypertension in elderly subjects: "STOP-Hypertension confirms that persistent diastolic hypertension in elderly people should be treated.....The results of SHEP indicate that blood pressure should be lowered if the systolic pressure averages 160 mm Hg or higher during long-term observation, irrespective of the diastolic pressure.....Blood pressure should probably be lowered irrespective of age provided the prospect of longevity is good from all other points of view."

Even though voices for the need for caution have been raised in letters to the JAMA (November 27, 1991) and Lancet (January 25, 1992), the

potential to prevent about 24,000 strokes and 44,000 major cardiovascular events in the United States every year just in those with ISH has led to a clear call for immediate application of these trials' results to the larger population (Stamler et al, 1991).

The Data from Controlled Trials

Six large placebo-controlled trials of treating elderly hypertensives have now been published and another trial among elderly with ISH is in progress in Europe. In the last year, 3 large trials have been added to the 3 small studies previously reported (Beard et al, 1992) (Table 6).

Table 6: Features of Six Trials of Hypertension in the Elderly

	Australian (Management, 1981)	EWPHE (Amery et al, 1985)	Coope and Warrender (1986)	STOP-Hypertension (Dahlof et al, 1991)	MRC (1992)	SHEP (1991)
No of patients	582	840	884	1627	4396	4736
Age range (years)	60-69	60-97	60-79	70-84	65-74	70-≥80
Blood pressure entry criteria:						
Systolic	<200	160-239	190-230	180-230 or <180	160-209	160-219
Diastolic	95-109	90-119	105-120	90-120 or 105-120	<115	<90
Mean blood pressure at entry	165/101	182/101	197/100	195/102	185/91 (43% ISH)	170/77 (100% ISH)
Blood pressure goal:					<160/<150*	<160/120*
Systolic			<170	<160		
Diastolic	<90<80**	<90	<105	95		
Treatment:						
Initial	Chlorthalidone	Hydrochlorothiazide + triamterine	Atenolol	Hydrochlorothiazide + amiloride Or Atenolol or metoprolol or pindolol	Hydrochlorothiazide + amiloride or Atenolol	Chlorthalidone
Add on	Various	Methyldopa	Bendrofluazide Methyldopa	Atenolol or metoprolol or pindolol Hydrochlorothiazide + amiloride	Atenolol or Hydrochlorothiazide + amiloride	Atenolol
Blood pressure obtained:						
Treatment group	143/87	149/85	162/77	167/87	152/79	
Placebo group	155/94	172/94	180/88	186/96	167/85	

*Depending on entry systolic pressure. **Initial goal < 90 mm Hg, reduced to < 80 mm Hg after two years ISH = Isolated Systolic Hypertension
(From Beard et al, 1991)

The overall results on stroke, coronary disease, congestive failure and all cardiovascular disease *events* are shown in Table 7.

Table 7: Effects of Therapy in Elderly Hypertensive Patients

	Australian	EWPHE	Coope & Warrander	STOP-HT	MRC	SHEP
Mean BP at entry	165/101	182/101	197/100	195/102	185/91 (43% ISH)	170/77 (100% ISH)
Events per 1000 patient years (Treated versus Placebo)/Relative Risk						
Stroke	.67	.64*	.58*	.53*	0.75*	.67*
Coronary disease	.82	.80	1.03	.87+	.81‡	.73*
Congestive failure		.78	.68	.49*		.45*
All cardiovascular	.69	.71*	.76*	.60*	.83*	.68*

* statistically significant + MI only ‡ Ischemic heart disease

The 3 previously reported trials were of fairly small size and, although they showed uniform protection against strokes, they differed in their effects on coronary disease (Management Committee, 1981; Amery et al, 1985; Coope and Warrender, 1986). Coronary mortality was significantly reduced in the EWPHE trial possibly because of protection against hypokalemia provided by the concomitant use of a potassium-sparing agent with the diuretic (Amery et al, 1990).

SYSTOLIC HYPERTENSION IN THE ELDERLY PROGRAM (SHEP, 1991) (Table 8)

Table 8: Systolic Hypertension in the Elderly Program (JAMA 1991;265:3255-64)

After screening 450,000 persons enrolled
4736 men and women (57%); (14% black)
3161 not previously on antihypertensive therapy
Average age = 71.6 (60 - 80+)
Average blood pressure = 170/77
No limitation of activities of daily living - 95%
Baseline ECG abnormalities - 61%

This was the first study to address the issue of isolated systolic hypertension (ISH), the most common form of hypertension in the elderly. To obtain the desired number of subjects, 450,000 people were screened. Note in particular, the relatively healthy state of those who were enrolled which brings up the question of the applicability of these data to the larger population of elderly hypertensives who are not so otherwise healthy, i.e. most of the 445,000 who were not enrolled after screening.

Table 9: Therapeutic Regimen of the Systolic Hypertension in the Elderly Program*

Random assignment to placebo or drug:		
1.	Chlorthalidone	12.5 mg q a.m.
2.	Chlorthalidone	25 mg q a.m.
3.	+ Atenolol	25 mg q a.m.
	or Reserpine	0.05 mg q a.m.
4.	+ Atenolol	50 mg q a.m.
Placebo treated switched to drug if BP > 240/115 X 1 or 220/90 sustained		
After 1 year, 90% *active*, 19% *placebo* on drug		
After 5 years, 90% *active*, 44% *placebo* on drug		

*data extracted from SHEP Cooperative Research Group. JAMA 1991;265:3255-64

The treatment protocol started with low doses of the long acting diuretic chlorthalidone (Table 9). If that was not enough, a low dose of a beta-blocker was added and by the end of the trial, about one-third were on both medications. In addition, almost half of the placebo-group had to be switched to drug therapy because of a rise in blood pressure beyond the acceptable upper limit. This admixture likely dilutes the strength of the protection found by the end of the study. Nonetheless, those on drugs had considerably less morbidity and mortality than did those on placebo (even though almost half were taking drugs) (Table 10).

Table 10: Results of the Systolic Hypertension in the Elderly Program*

	Active	Placebo
Number of patients	2365	2371
Mean BP at 5 years (mm Hg)	144/68	155/71
Fall from baseline	-27/9	-16/6
Number of events (relative risk)		
- Strokes	96	149 (0.63)
Stroke deaths	10	14 (0.71)
- Myocardial infarction	50	74 (0.67)
CAD deaths	59	73 (0.80)
- Left ventricular failure	48	102 (0.46)
- Noncardiovascular deaths	109	103 (1.05)

*data extracted from SHEP Cooperative Research Group. JAMA 1991;265:3255-64

Side effects were increased in those on drugs and they were characterized as "intolerable" in 28.1% of those on drug therapy compared to 20.8% of those on placebo. However, medication had to be stopped because of side effects in only 13% of those on drug therapy compared to 7% of those on placebo.

SWEDISH TRIAL IN OLD PATIENTS WITH HYPERTENSION (STOP-HYPERTENSION) (Dahlof et al, 1992)

This trial involved 1627 patients aged 70-84 with a systolic blood pressure between 180 and 230 mm Hg and with a diastolic of at least 90 or a diastolic between 105 and 120 irrespective of the systolic pressure, i.e., only patients with combined systolic + diastolic hypertension (Table 11).

Table 11: Swedish Trial in Old Patients with Hypertension (Dahlöf et al. Lancet 1991;338:1281)

- 1627 men (37%) and women aged 70-84 (mean = 75.7)
- Mean blood pressure (supine) = 195/102
- Double-blind random allocation to placebo or therapy of:
  - atenolol 50 mg
  - HCTZ 25 mg + amiloride 2.5 mg
  - metoprolol 100 mg
  - pindolol 5 mg
- If BP > 160/95 after 2 months, diuretic + beta-blocker

The protocol involved random allocation of half of the patients to placebo and the other half to one of 4 drugs: a diuretic + potassium sparer or one of 3 beta-blockers. There is no information as to how many patients were assigned to which. However, since the majority (68%) of all patients on drug therapy ended up on a combination of one of the three beta-blockers plus the diuretic and K-sparer to achieve the goal of a supine blood pressure below 160/95, there will be no sub-group analysis.

Table 12: Results of the Swedish Trial in Old Patients with Hypertension

	Active	Placebo
Number of patients	812	815
Mean BP at end (mm Hg)	167/87	186/96
Fall from baseline	-28/15	-9/7
Number of events (relative risk)		
Strokes	29	53 (0.53)
Stroke deaths	3	12 (0.24)
Myocardial infarction	25	28 (0.87)
MI deaths	6	6 (0.98)
Other cardiovascular deaths	4	13 (0.30)
Left ventricular failure	19	39 (0.49)
Total mortality	36	63 (0.57)

The results show a significant reduction in stroke morbidity and mortality, total mortality, and episodes of CHF but no effect on acute MI events or deaths. However, "other cardiovascular deaths" which included sudden deaths, were reduced from 13 in the placebo half to 4 in the drug-treated half (Table 12). In addition, rises of blood pressure to above 230/120 occurred in 75 of the placebo group and only 10 of the drug group. Benefits were seen in all age groups.

MEDICAL RESEARCH COUNCIL (MRC) TRIAL OF TREATMENT OF HYPERTENSION IN OLDER ADULTS (MRC, 1992)

The MRC's general practice research framework involving 226 practices throughout Britain was used to identify 4396 subjects aged 65 to 74 with systolic pressure of 160-209 mm Hg and diastolic pressure of 114 mm Hg or less on the third set of readings during an 8 week run-in while on no treatment (Table 13). The average starting blood pressure was 185/91 and fully 43% of the study population had pure systolic hypertension, i.e., diastolic pressure below 90 mm Hg. The subjects were randomly allocated in equal numbers to either hydrochlorothiazide 25 mg plus amiloride 2.5 mg or matching placebo or to atenolol 50 mg or matching placebo. Depending on how high the pressures were initially, the goal of therapy was to reach a systolic level of either 150 to 160 mm Hg and this could be accomplished in this order: doubling the dose of initial drug, adding the other trial drug, or starting nifedipine and other supplementary drugs. Follow-up averaged 5.8 years.

Table 13: MRC Trial of Treatment of Hypertension in Older Adults (BMJ 1991;304:405-12)

4396 patients; 42% men; aged 65-74 (mean = 70.3)

BP: systolic 160-209, diastolic < 115, average @ 185/91
- 43% with DBP < 90, i.e., isolated systolic HT

Random assignment to placebo or one of two drugs
- HCTZ 25 mg + amiloride 2.5 mg or atenolol 50 mg

Supplemental Rx if systolic not reduced to 150 or 160
- increase atenolol to 100; add other drug; add nifedipine
- at 5 years, needed by 52% on β-blocker, 38% on diuretics

Both Rxs lowered BP significantly below placebo:
- placebo -167/85; Drug -152/79

Average followup = 5.8 years

The systolic and diastolic pressures fell rapidly, with a greater immediate reduction in systolic levels in those on the diuretic. To achieve the goal blood pressure, 52% of those on β-blocker and 38% of those on diuretic had to be given supplementary drugs by the fifth year.

By the end of the study, about 25% of the subjects had been lost to follow-up and even more had stopped taking their randomized treatment so that more than half of the study population were not on their prescribed therapy. Despite these dropouts and withdrawals, there were significant 25% decreases in fatal and non-fatal strokes and an almost significant 19% reduction in coronary events. Although deaths from cardiovascular causes were slightly fewer in the treated group than the placebo group (161 versus 180), all cause mortality was similar, in large part because of more cancer deaths in those given β-blocker.

Subgroup analysis of the two treatment groups separately showed significantly fewer coronary events and cardiovascular events and deaths in those given diuretic than in those given β-blocker (Figures 7 and 8). Reduction in stroke events was confined to non-smokers but coronary events and all cause mortality did not differ between smokers and non-smokers. However, the effect of the β-blocker on all cause mortality was significantly reduced by smoking when compared with the effect of the diuretic.

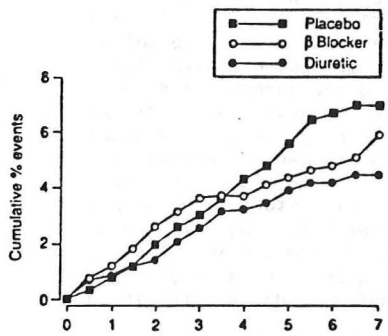

Figure 7: Cumulative percentage of patients experiencing stroke by randomised treatment. (From MRC Working Party, 1992)

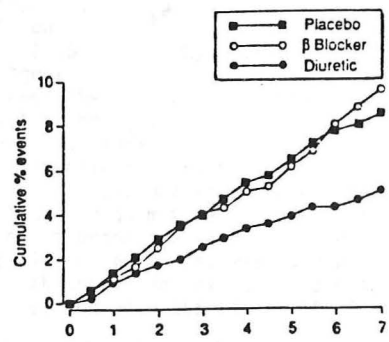

Figure 8: Cumulative percentage of patients experiencing coronary events by randomised treatment. (From MRC Working Party, 1992)

As shown in these figures, the most striking finding of this trial is the much greater effect of diuretics in preventing coronary events and deaths, whereas the β-blocker gave no protective effect against any end point and was associated with an increased mortality from cancer. The authors offer a number of possibilities for "this interesting finding (that) is contrary to expectations." These include only a small (0.1 mmol/L) increase in serum cholesterol, the lower dose of diuretic and concomitant use of a potassium-sparing agent, the more rapid and greater control of blood pressure with the diuretics, and differences in the nature of hypertension and responses to treatment in the elderly.

The high rates of drop out and withdrawal, although likely inherent in the nature of this study design, are of concern. Similarly, the high rate of admixture of drugs to achieve the goals of therapy becloud the purity of the data. Nonetheless, the striking differences between the diuretic and β-blocker group must be significant, not just statistically but clinically as well.

This is the conclusion of the six British hypertension experts whose analysis of the six published randomized trials of the treatment of hypertension in elderly patients follows the report of the MRC trial (Beard et al, 1992). After delineating the differences in various features of the patients enrolled and the therapies used (see Table 6), they point to several overall trends that are apparent (see Table 7). Stroke events were reduced in all six, significantly in five. Coronary events were also reduced but to a lesser degree and significantly in only one, the Systolic Hypertension in the Elderly Program.

The authors make a number of recommendations on the basis of these data, including:

- treatment should be considered for patients up to age 80 with systolic pressure about 160 mm Hg
- the goal of therapy should be a blood pressure below 160/90
- non-pharmacological measures should be utilized, particularly a modest reduction in salt intake and a higher intake of dietary potassium
- the choice of antihypertensive therapy should be based upon the presence of concomitant conditions (Table 14), individualizing therapy rather than using the stepped care approach
- first-line therapy for those with uncomplicated hypertension should be low doses of a diuretic, e.g., 12.5 mg/d of hydrochlorothiazide, likely with a potassium-sparing agent
- β-blockers "cannot now be considered the treatment of choice in elderly hypertensive patients," although they may be used in those with angina or a prior myocardial infarction
- even though the newer agents (angiotensin converting enzyme inhibitors, calcium entry blockers, alpha-blockers) have not been subjected to controlled trials, "such drugs may be favored on a number of theoretical and practical grounds, particularly when diuretics or β-blockers are contraindicated. They may have a major role in managing patients with coexistent disease, such as heart failure, chronic lung disease, and diabetes (Table 14)."

Table 14: Selection of Antihypertensive Drug Treatment According to Coexisting Disease in Elderly Patients

Coexisting disease	Diuretic	β-Blocker	calcium blocker	Angiotensin converting enzyme inhibitor
None	++	+	+	+
Heart failure	++	-	-	++
Angina	+	++	++	+
Asthma or chronic obstructive airways disease	++	-	+	+
Peripheral vascular disease	+	-	++	-*
Gout	-	+	+	+
Diabetes	-	-	+	++

++ = First line drug; + = Suitable alternative drug; - = Usually contraindicated; * High proportion of patients with peripheral vascular disease will have occult renovascular disease
(From Beard et al, 1992)

This succinct summary offers strong support for the treatment of hypertension in most elderly patients, unless they have serious other diseases that "dominate the clinical picture." Such therapy has been shown to provide benefits that are "considerably greater than those conferred by treating younger patients." These recommendations, including the use of small doses of drugs with gradual reduction of pressure and avoidance of postural hypotension, seem to be excellent guidelines for all to follow in treating this rapidly expanding population of elderly patients at increased risk from hypertension.

Additional Considerations in the Choice of Drugs

The list of concomitant conditions frequently found in elderly patients is obviously far longer than shown in the preceding table. There are others which serve as relative or absolute contraindications to the use of specific drugs.

Table 15: Contraindications to Specific Drugs

Condition	Drug Contraindicated
Postural hypotension, cerebro-vascular disease	Posturally acting drugs (e.g. adrenergic-neuron blockers)
Chronic obstructive pulmonary disease	Beta-blockers
Atrioventricular block (2nd or 3rd degree)	Beta-blockers, verapamil
Congestive heart failure	Beta-blockers*
Hypertensive hypertrophic cardiomyopathy	Diuretics, ACEIs
Peripheral vascular disease	Beta-blockers
Angina, tachycardia	Direct vasodilators
Depression	Reserpine, methyldopa, clonidine, lipid-soluble beta-adrenoceptor blockers (?)
Headache	Calcium antagonists
Hyperuricemia, gout	Diuretics*
Impaired glucose tolerance, diabetes	Diuretics*
Hypokalemia	Diuretics*
Liver disease	Methyldopa
Constipation	Verapamil
Unreliable taker of tablets	Clonidine
Bilateral renal artery stenosis	ACE inhibitor
Systemic lupus erythematosus	Hydralazine, methyldopa
Taking beta-adrenoceptor blocker	Verapamil
Taking verapamil	Beta-adrenoceptor blocker

*Relative contraindication

(From Simpson FO. Choice of antihypertensive drugs in the elderly. IN Amery A, Staessen J, eds. Handbook of Hypertension, vol 12: Hypertension in the Elderly. Elsevier Science Publishers, 1989:368-86)

In the face of the relatively shrunken vascular volume and high peripheral resistance that are the hemodynamic features of hypertension in the elderly, the use of vasodilating drugs seems attractive rather than diuretics which initially act by further reducing intravascular volume or beta-blockers which reduce cardiac output and further raise peripheral resistance (Weber et al, 1989). Nonetheless, in the absence of any data on the effectiveness of other agents than diuretics or beta-blockers to reduce cardiovascular morbidity and mortality, the advocacy of these two "old-fashioned" classes of drugs is gaining momentum both in England and in the United States. A major additional point in their favor is their low cost, keeping in mind that the cost of the tablet may not reflect the total cost of the medication. Certainly, if other agents cost more but need less laboratory testing and ancillary therapies to correct the mischief they induce, i.e., K+ supplements or hypolipidemic drugs, the relative cost of the more expensive newer drugs could be less than the simple cost of the tablets would suggest.

As different drugs are considered, we should remember that for the universe of hypertensives, they are equally effective in usual doses. The doses recommended are those needed for the 10% reduction in blood pressure in about 70% of those tested that is needed for FDA approval. Side effects vary but, in today's over-crowded market, agents with really bothersome and dangerous side effects such as guanethidine and methyldopa would likely never have been marketed.

Despite their overall equality in effectiveness, individual drugs work somewhat differently in certain groups, e.g., beta-blockers and ACEIs are less effective in blacks. Moreover, individual patients respond differently to different drugs often with no obvious reason. Therefore, if the first choice does not work well, the wisest move is to stop it and substitute another of a different class rather than adding on in the old "stepped-care" approach (Kaplan, 1992).

Diuretics

Diuretics may work somewhat better in the elderly (Freis et al, 1988) perhaps because sodium sensitivity progressively increases with age (Weinberger and Fineberg, 1991). They work equally in whites and blacks. The major recent change in their use is the recognition that much lower doses, i.e., 12.5 to 25 mg per day of hydrochlorothiazide or chlorthalidone, will work as well as much larger doses in most patients while causing significantly fewer biochemical aberrations (Morledge et al, 1986; Carlsen et al, 1990; Materson et al, 1990; Cushman et al, 1991).

In addition to their cheapness and relative freedom from overt side effects, diuretics may offer protection from fractures related to osteoporosis by reducing urinary calcium excretion (LaCroix et al, 1990). However, some report no such benefit (Heidrich et al, 1991).

Despite the current renewed enthusiasm for their use, concerns remain: even low doses of diuretics can worsen serum lipids and the effect may last for years (Treatment of Mild Hypertension, 1991) and diuretic usage was associated with a marked increase in mortality among diabetic hypertensives treated in the late 1970s at the Joslin Clinic (Warram et al, 1991). Nonetheless, in appropriately low doses and

preferably with potassium sparers, diuretics will continue to be the most widely used drug to treat the elderly hypertensive for the foreseeable future.

Alpha-blockers

As will be authenticated in the 1992 Fifth Joint National Committee Report, an alpha-blocker is an appropriate choice in those who should not be given or who do not respond well to a diuretic. They are equally effective in the elderly and the newer longer acting agents (doxazosin and terazosin) are less likely to cause first-dose or later postural hypotension (Scott et al, 1988).

For elderly men with benign prostatic hypertrophy, alpha-blockers offer considerable relief from the obstructive symptoms of prostatism and are widely used by most urologists for this (unapproved) purpose (Lepor, 1989). For those men with both a large prostate and high blood pressure, an alpha-blocker would be a logical choice, particularly since it will likely also improve the lipid profile and improve insulin sensitivity (Khoury and Kaplan, 1991).

Beta-blockers

These agents offer multiple special features: relief of angina, migraine, essential tremor, and glaucoma as well as secondary protection after an MI. However, the lack of primary protection against the first MI by atenolol in the 1992 MRC trial in the elderly (see Figure 8) casts a major doubt about their use. Moreover, they may make it more difficult for the elderly to perform physical activity.

The combined alpha-beta blocker labetalol has been shown to be both effective and well tolerated in elderly patients (Applegate et al, 1991).

Calcium Entry Blockers

These drugs will likely become the second most widely used drug for elderly hypertensives, in part because of a widely held but incorrect view that they are especially effective in the elderly, a view promulgated by Buhler (1988) but not documented in most comparative studies (Kaplan, 1989; Ling et al, 1991).

Nonetheless, calcium blockers do work well in the elderly and are generally well tolerated. However, in a randomized, double-blind crossover trial with 31 elderly hypertensives, atenolol and nifedipine had no gross effects on psychometric tests designed to assess mood and cognitive function but nifedipine (which lowered the blood pressure more than did the atenolol) caused subtle impairments of learning and memory in some patients (Skinner et al, 1992).

ACE Inhibitors

ACEIs are also effective in the elderly (Freis et al, 1988) and the increasing evidence that they provide additional myocardial and renal protection will likely translate into continued growth in their use in hypertensives of all ages. Moreover, they may provide even better regression of left ventricular hypertrophy than other drugs (Dahlof et al

1992). Whether greater regression of LVH will translate into less coronary mortality remains to be seen.

Other Agents

Central alpha-agonists certainly are effective in the elderly (Carruthers, 1988) but I find them less attractive than other agents because of the sedation and dry mouth that often occur with their use.

Sustained-release isosorbide dinatrate was found to be quite effective and well tolerated in a group of 40 elderly patients with ISH (Duchier et al, 1987). With the growing awareness of the importance of nitric oxide (NO) as the endothelium derived relaxing factor, additional agents which increase NO will likely become available.

Combination Therapy

The combination of low doses of two agents has the potential for greater antihypertensive efficacy with fewer dose-related side effects. This has been shown for the combination of an ACEI (enalapril) and a calcium blocker (felodipine) in a double-blind, three-way crossover study of 36 elderly hypertensives (Morgan et al, 1992).

CONCLUSION

The more active treatment of the rapidly growing population of elderly hypertensives will likely become an increasingly common practice, offering both the promise of longer preservation of health and mobility but at the same time the peril of overly-aggressive reduction of perfusion to vital organs. The need to follow reasonable guidelines (Table 16) to avoid overtreatment is critical.

Table 16: Guidelines in Treating Hypertension in the Elderly

1. Check for postural and postprandial hypotension before starting
2. Choose drugs that will help other concomitant conditions
3. Start with small doses, titrating gradually
4. Use longer acting, once daily formulations
5. Avoid drug interactions, particularly from over-the-counter medications, e.g., NSAIDs
6. Look for subtle drug-induced adverse effects, e.g., weakness, dizziness, depression, confusion
7. Monitor home blood pressures to avoid over and under treatment
8. Aim for the goal of SBP = 140-145, DBP = 80-85
9. Contact patient or family if appointments are missed

The need for special care in treating the elderly was rather eloquently described in a piece in the April 1, 1992 JAMA (267:1750) by a Yale house officer:

> "Before she was reassigned to me, 82-year-old Mrs Hines had been treated by a departing resident. He had dutifully forewarned me that this patient had several stable medical problems and was on an archaic medical regimen that, contrary to good medical judgement, seemed to suit her just fine.

".....With some effort and diplomacy I refocused our discussion on her medical problems, noting anxiously that her systolic blood pressure was elevated to 194. I scanned her medical record and discovered that her blood pressure had been elevated during several previous clinic visits and that her medical regimen was woefully inadequate, with many of the prescribed doses being homeopathic. I explained to her the need to change her medications and promptly wrote a prescription for a potent, new antihypertensive agent. 'Are you sure?' she appealed to me. 'My last doctor always said I was doing so well.'

"I took her hand and reassured her, 'I would feel uncomfortable not making a change at this time. The new blood pressure medicines are more effective and have fewer side effects than the older ones.'

"She smiled, picked up the prescription, and studied it intently. 'I guess I can give it a try.'

"Of course I knew best. The potential consequences of long-standing hypertension, especially when poorly controlled, are myriad. But somehow, blinded by professional hubris, I had neglected to appreciate that Mrs Hines, without my assistance, had lived to be a spry octogenarian.

"One day later [the patient was admitted after falling at home, when her systolic blood pressure was found to be 90].....Mrs. Hines seemed happy to see me as I entered her hospital room the following morning. 'That's my doctor,' she pointed out proudly to the nurse who was taking her blood pressure. I asked her to explain what had happened. She stated that within one hour of taking the new medication she didn't feel well, experiencing 'cold sweats' and a sensation of 'seeing lights, like colored medallions.' She must have noticed the look of remorse on my face, for she declared, 'You mustn't blame yourself. I guess I'm just sensitive to new medicines. I've always been that way, you know.' No, I didn't know. I hadn't taken the time to know.

"Mrs. Hines was discharged from the hospital after three days. Fortunately, she sustained no long-lasting ill effects from her hypotensive episode. For three years, I have followed her in my clinic, and her systolic blood pressure has remained elevated. She takes all of her previous medications at their former homeopathic but effective doses, and I have renewed this regimen on a quarterly basis. I saw her for the last time two weeks ago. We reminisced about our initial encounters together. I had just informed her that I would be leaving the clinic in two months, and that she would be reassigned to a new doctor. This time she took my hand in hers, perhaps perceiving my sense of loss and sadness. Several seconds passed in silence. Finally, her face brightened and she smiled. 'I guess I'll have to break in another one.'"

T.M. Gill (1992)

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