MEDICAL GRAND ROUNDS

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Improving Our Currently Inadequate Management of Hypertension

by

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Despite the facts that hypertension is the most common indication for office visits to physicians and for the use of prescription drugs in the U.S. today (Woodwell, 1997), the percentage of Americans whose hypertension is well-controlled remains below 30% and may be falling (Joint National Committee [JNC-6] 1997) (Table 1).

Table 1. TRENDS IN THE AWARENESS, TREATMENT, AND CONTROL OF HIGH BLOOD PRESSURE IN ADULTS: UNITED STATES, 1976-94*

	NHANES II 1976-80	NHANES III (Phase 1) 1988-91	NHANES III (Phase 2) 1991-94
Awareness	51%	73%	68%
Treatment	31%	55%	53%
Control (BP < 140/90)	10%	29%	27%

* Data are for adults age 18 to 74 years with SBP of 140 mm Hg or greater, DBP of 90 mm Hg or greater, or taking antihypertensive medication.
(From JNC-6 Arch Intern Med 1997;157:2413-2446)

Likely in part because of the flattening or falling rates of hypertension control, the declines in mortality from strokes observed over the last 30 years have slowed and the rates for two diseases often related to hypertension - end-stage renal disease (U.S. Renal Data, 1997), and congestive heart failure (Levy et al., 1996), have continued to increase steadily (Figures 1A and 1B).

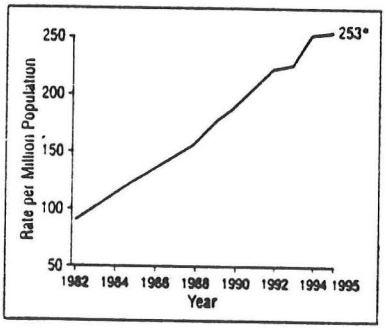

Figure 1A. Incidence rates per million population of reported end-stage renal disease therapy. 1982 to 1995, adjusted for age, race, and sex. Asterisk indicates provisional data. Source: US Renal Data System, 1997.

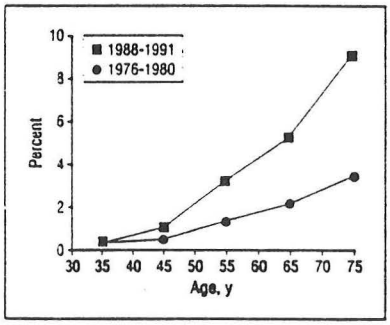

Figure 1B. Prevalence of congestive heart failure, by age, 1976-1980 and 1988-1991. Source: National Health and Nutrition Examination Survey (1976-1980 and 1988-1991), National Center for Health Statistics.

There are many reasons for the inadequate control of hypertension, not the least being the inherent nature of the disease: a chronic but asymptomatic condition whose treatment entails considerable expense and often interferes with the quality of life and that provides benefits that are apparent, if at all, only after many years. I will examine, first, the population-wide maneuvers that may help improve upon our currently inadequate control of hypertension and then apply those and other maneuvers to the management of an individual patient.

POPULATION-WIDE MANEUVERS

Primary Prevention

As stated in JNC-6: "Without primary prevention, the hypertension problem would never be solved and would rely solely on detection [and treatment] of existing high blood pressure. Primary prevention provides an attractive opportunity to interrupt and prevent the continuing costly cycle of managing hypertension and its complications. Primary prevention reflects many realities:

- A significant portion of cardiovascular disease occurs in people whose blood pressure is above the optimal level (120/80 mm Hg) but not so high as to be diagnosed or treated as hypertension. (Kannel, 1996) A population-wide approach to lowering blood pressure can reduce this considerable burden of risk.

- Active treatment of established hypertension, as carefully as can be provided, poses financial costs and potential adverse effects.

- Most patients with established hypertension do not make sufficient lifestyle changes, do not take medication, or do not take enough medication to achieve control. (Burt, et al., 1995)

- Even if adequately treated according to current standards, patients with hypertension may not lower their risk to that of persons with normal blood pressure. (Thurmer et al., 1994)

- Blood pressure rise and high blood pressure are not inevitable consequences of aging. (Stamler, 1991)

Therefore, an effective population-wide strategy to prevent blood pressure rise with age and to reduce overall blood pressure levels, even by a little, could affect overall cardiovascular morbidity and mortality as much as or more than that of treating only those with established disease (Rose, 1992)."

1. Avoidance of obesity: Obviously, Americans, including the young, are becoming increasingly obese (Flegal et al., 1998) and obesity is involved in most hypertension (Kannel et al., 1993). Since treatment of established obesity is so difficult, prevention is essential but may be impossible with the high calorie diet and minimal physical activity that are typical of modern America.

   Additionally, the ability of lifestyle changes to significantly reduce the incidence of hypertension in those who are already overweight and those who have high-normal BP has been difficult to document (Trials of Hypertension Prevention, 1997) (Figure 2). However, reductions in BP over various intervals and decreases in the incidence of hypertension have been documented even in those who achieve relatively little long-term improvement in lifestyles (Neaton et al., 1993; Appel et al., 1997).

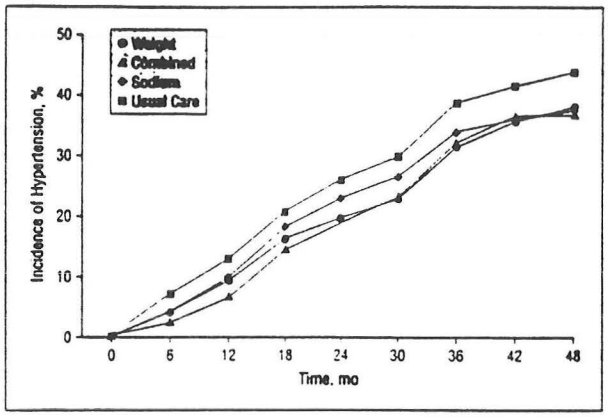

Figure 2. Plot of the incidence of hypertension for the respective randomized groups through 48 months of follow-up, from life-table analysis in the Trials of Hypertension Prevention, Phase II. (Source: Trials of Hypertension Prevention, 1997).

The critical importance of avoiding weight gain has been documented in the 16-year follow-up of 82,473 initially normotensive nurses aged 30 to 55 (Huang et al., 1998). The gain of from 5 to 10 kg from the weight at age 18 almost doubled the risk for the development of hypertension and 48% of the risk for hypertension was attributable to long-term weight gain. The progressive increase in risk was greater in older women, perhaps because they also lost lean body mass as they aged (Figure 3).

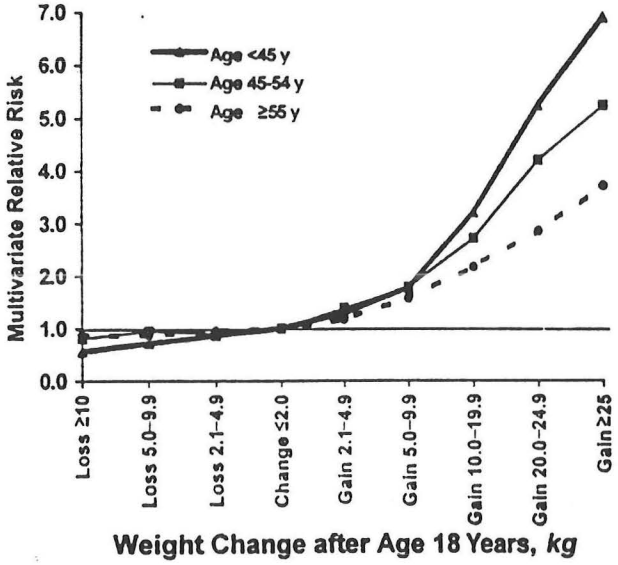

Figure 3. Multivariate relative risk for hypertension according to weight change after age 18 years within strata of age. Adjusted for age, body mass index at age 18 years, height, family history of myocardial infarction, parity, oral contraceptive use, menopausal status, postmenopausal use of hormones, and smoking status (Source: Huang et al., 1998).

2. Increase physical activity: Beyond its essential role in prevention of obesity, physical activity may lower blood pressure independently. As found among people followed at the Cooper Aerobic Center, sedentary individuals with normal BP have a 20 to 50% increased risk of developing hypertension compared with those who are more active and fit (Blair et al., 1984). Similarly, the incidence of hypertension over a 40-year follow-up was reduced almost by half in those medical students who engaged regularly in sweat-inducing physical activity (Lowry et al., 1995).

3. Moderation of sodium intake: Despite the warnings of some who are concerned about possible dangers from reduced sodium intake (Alderman, 1997), there is overwhelming evidence of an essential, though not in itself sufficient role of our current high sodium intake in the pathogenesis of primary hypertension (Kaplan, 1998). The degree of dietary restriction that is widely

recommended - no more than 2.4 g/d of sodium (6 g/d of sodium chloride) - can be only achieved by avoidance of processed foods that have more than 300 mg of sodium in each portion since 80% of sodium intake in the U.S. is non-discretionary, i.e., already in the processed food and not added in the preparation or at the table (Engstrom et al., 1997).

4. Moderation of alcohol: Too much alcohol causes hypertension and much more; too little alcohol increases the risk of coronary disease (Thun et al., 1997) (Figure 4). Part of the protection by regular consumption of small amounts of ethanol may reflect increased insulin sensitivity (Kiechl et al., 1996).

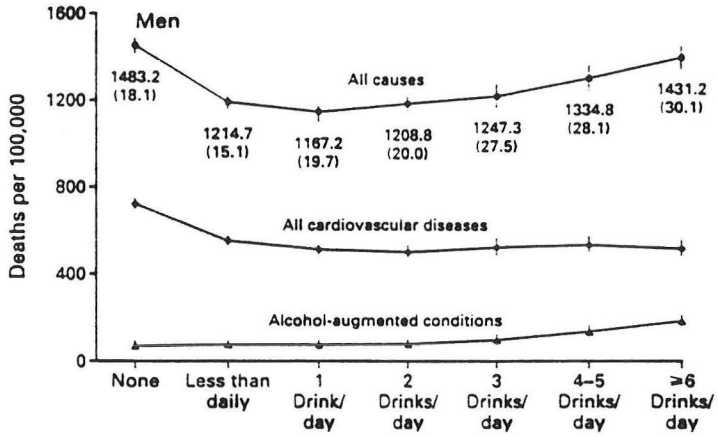

Figure 4. Rates of death from all causes, all cardiovascular diseases and alcohol - augmented conditions from 1982 to 1991 among 238,206 U.S. men acording to alcohol consumption in 1982 Source: Thun, et al., 1997)

5. Avoidance of cigarette smoking: The transient but significant pressor effect of smoking (Groppelli et al., 1992) (Figure 5) may be missed if the blood pressure is taken 30 minutes or longer after the last cigarette. Those who smoke 20 or more per day have a persistent rise in BP (Verdecchia et al., 1995). There should be no pressor effect from the small amounts of nicotine in the patches, gums, and sprays used as aids in smoking cessation (Khoury et al., 1996).

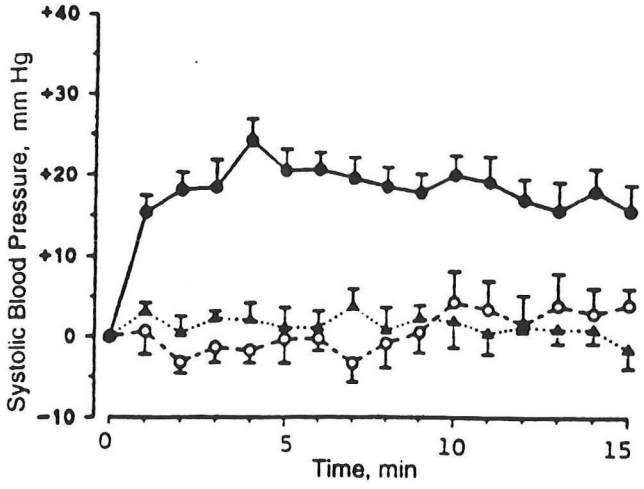

Figure 5. Changes in systolic blood pressure over 15 min after smoking the first cigarette of the day, within the first 5 minutes (solid circles), during no activity (open circles), and during sham-smoking (triangles) in 10 normotensive smokers. (Source: Groppelli et al, 1992).

6. Surveillance of blood pressure: There should be increased emphasis on measuring BP regularly both to screen for hypertension and, more importantly, to recognize "less than optimal" blood pressure levels so that preventive measures can be introduced earlier. Since out-of-the-office BP readings avoid the white-coat effect, every household should have a BP device as well as a thermometer.

7. Earlier intervention with medications: As cardiovascular epidemiologists have emphasized, the "normal" blood pressure is well below 140/90, with progressively lower rates of coronary disease and stroke with progressively lower levels of blood pressure (MacMahon et al., 1990) (Figure 6).

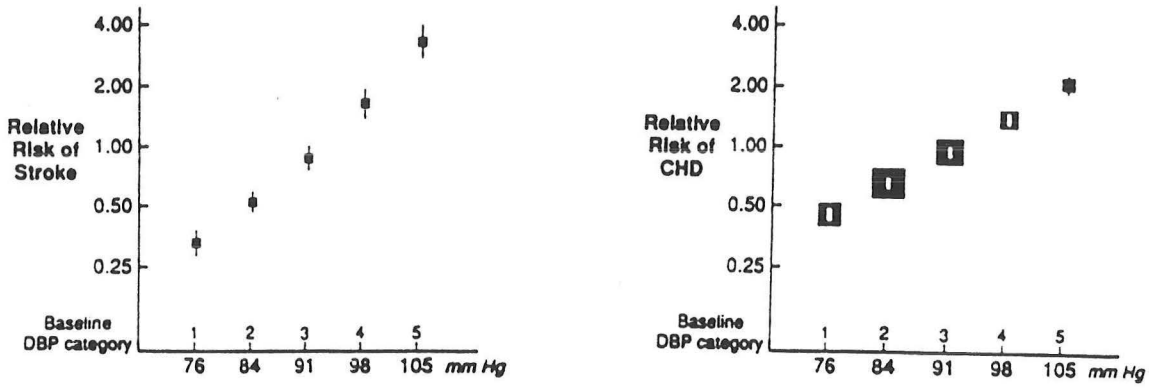

Figure 6. Relative risk of stroke (A) and CHD (B), estimated from the combined results of prospective observational studies for five categories of DBP. (Estimates of the usual DBP in each baseline DBP category are from mean DBP values in the Framingham study recorded 4 years after baseline measurement.) The stroke data were obtained from seven prospective observational studies; n=843 events. The CHD data were obtained from nine prospective observational studies; n=4856 events. The solid squares represent disease risk in each category relative to risk in the whole study population (square size is proportional to the number of events in each DBP category). Vertical lines represent 95% confidence intervals for the estimates of relative risk. Source: MacMahon et al., 1990).

The evidence that treatment of high-normal blood pressure reduces these rates of cardiovascular (CV) disease has not been obtained, so that most expert committees recommend drug therapy only for those with definite hypertension or with high-normal BP in the presence of other major risk factors or existing CV disease (JNC-6, 1997).

However, the evidence from short-term (3 to 7 year) trials may not portray the long-term benefits. For example, data from the Framingham Heart Study support a much greater efficacy of antihypertensive drug therapy over longer periods (Sytkowski et al., 1996). Successive cohorts of hypertensive patients aged 50 to 59 were followed for 20-year intervals, starting in either 1950, 1960, or 1970. The evidence of cardiovascular disease was detected during the first 10 years of follow-up of each cohort, and mortality was assessed during the second 10 years (Table 2). The percentages of all-cause mortality and cardiovascular mortality were similar in the 1950 cohort whether they were on treatment for hypertension or not. However, both the 1960 and 1970 cohorts who were treated had significantly fewer deaths during follow-up than did the untreated patients. Overall, the risk of all-cause mortality was reduced by 31% and the risk of cardiovascular mortality was reduced by 60% among those on long-term therapy.

Table 2. Mortality among Long-Term, Sustained Hypertensive Patients during the Second 10 Years of Follow-up

Baseline	1950	1960	1970
Follow-up period	1960-1970	1970-1980	1980-1990
On treatment, percent death / CV death	41/26	29/10	31/9
Not on treatment, percent death / CV death	42/26	38/24	44/15

Secular trends in long-term sustained hypertension, long-term treatment, and cardiovascular mortality. The Framingham Heart Study 1950 to 1990. (Source: Sytkowski et al, 1996).

These results are much greater than those observed in the multiple short-term trials. Therefore, the authors' conclusion that the long-term benefits of the treatment of hypertension may be much greater than those seen in shorter-term clinical trials seems appropriate.

The problem has been well framed by Zanchetti and Mancia (1996) who first agreed that short-term trials are suitable to assess the efficacy of therapy when "a relatively high rate of events is expected during the time span of the trial." They go on to say:

"Using criteria derived from short-lasting event-based trials for assessing the benefits and the costs of antihypertensive therapy in young and middle-aged subjects with mild hypertension quantitatively is, however, inappropriate. In these subjects the goal of antihypertensive therapy is not to prevent an unlikely hypertension-related event during the next 3-6 years, but rather to prevent or retard the development of cardiovascular lesions and help the subjects to attain their full life span. Because therapeutic trials lasting 20-30 years have never been performed, and are not likely to be done, the possibility that calculations based upon actuarial life expectancy data may represent a more realistic far-sighted approach should be discussed."

When Zanchetti and Mancia (1996) apply the Metropolitan Life Insurance actuarial data on differences in life expectancy between normotensive and hypertensive subjects in the period between 1935 and 1954, before effective antihypertensive therapy was available, they conclude that therapy of even mild hypertension in younger people would be very cost-effective as for years of life gained (Table 3).

Table 3. Costs of Therapy per Year of line Gained in Men with a BP of 140/95. Based on Actuarial Life Expectancy Data[a]

Age	Normal Life Expectancy, Years	Reduced Life Expectancy, Years	Expected Benefits, Years of Life	Costs of Treatment, US $	Cost/Year Life Gained, US $
35	41.5	9.0	5.4	21,500	4,000
45	32.0	6.0	3.6	16,700	4,650
55	23.5	4.0	2.4	12,400	5,200

[a] The reduced life expectancy is based on the differences between normotensive and hypertensive people in the years 1935-1954 from the Metropolitan Life Insurance Co. actuarial data; the expected benefit is based on the assumption of complete reversibility of hypertension-attributable mortality from stroke and 50% from coronary disease and a coronary: stroke ratio of 4:1.
Modified from Zanchetti A. Mancia G. Benefits and cost-effectiveness of antihypertensive therapy. The actuarial versus the intervention trial approach. *J Hypertens* 1996;14:809-811.

Since we have not been able to document the long-term benefits of lowering even minimally elevated BP over periods of 3-6 years, active drug therapy for those with "less than optimal" BP cannot be currently advocated. Perhaps with drugs that have less inherent toxicity, such long-term benefits in low-risk hypertensive patients will be demonstrable in relatively short times, in a manner similar to what has been seen with the use of statins for treatment of patients with minimally elevated lipid levels.

Secondary Prevention

Once hypertension has developed, the BP must be lowered to below 140/90, perhaps much more than usually recommended. Here again, the data from short-term trials do not provide proof of long-

term needs. In three groups of patients at high risk of progressive target organ damage - those with diabetic nephropathy, congestive heart failure or post myocardial infarction - the use of certain antihypertensive agents has been shown to reduce mortality even without concomitant hypertension and without necessarily much, if any, reduction in blood pressure. These effects, seen primarily with angiotensin converting enzyme inhibitors (ACEI) and, to a lesser degree, with beta-blockers, may have little to do with these drugs' antihypertensive effects although some lowering of BP is usual when they are used even in normotensive patients.

The need for more aggressive lowering of BP than usually recommended has been seen particularly in patients with renal insufficiency (Toto et al., 1995, Lazarus et al., 1997). It may turn out that this experience is a window to the larger population but for now a goal of below 140/90 is generally recommended for uncomplicated hypertension (JNC-6, 1997).

1. Lifestyle Modifications: These are similar to those recommended for primary prevention (Table 4).

Table 4. Lifestyle Modifications for Hypertension Prevention and Management

Lose weight if overweight
Limit alcohol intake to no more than 1 oz (30 mL) of ethanol (eg, 24 oz [720 mL] of beer, 10 oz [300 mL] of wine, or 2 oz [60 mL] of 100-proof whiskey) per day or 0.5 oz (15 mL) of ethanol per day for women and lighter-weight people
Increase aerobic physical activity (30-45 min most days of the week)
Reduce sodium intake to no more than 100 mmol/d (2.4 g of sodium or 6 g of sodium chloride)
Maintain adequate intake of dietary potassium (approximately 90 mmol/d)
Maintain adequate intake of dietary calcium and magnesium for general health
Stop smoking and reduce intake of dietary saturated fat and cholesterol for overall cardiovascular health.

2. Institution of drug therapy: JNC-6 appropriately recognizes the importance of both concomitant risk factors and existing target organ damage or clinically overt cardiovascular diseases (Table 5) in addition to the level of blood pressure in deciding upon the need for antihypertensive drug therapy (Table 6).

Table 5. Components of Cardiovascular Risk Stratification in Patients with Hypertension

Major Risk Factors	Target Organ Damage/Clinical Cardiovascular Disease
Smoking	Heart diseases:
Dyslipidemia	- Left ventricular hypertrophy
Diabetes mellitus	- Angina/prior myocardial infarction
Age older than 60 years	- Prior coronary revascularization
Sex (men and postmenopausal women)	- Heart failure
Family history of cardiovascular disease: women under age 65 or men under age 55	Stroke or transient ischemic attack
	Nephropathy
	Peripheral arterial disease
	Retinopathy

Table 6. Risk Stratification and Treatment*

Blood Pressure Stages (mm Hg)	Risk Group A (No Risk Factors; No TOD/CCD†)	Risk Group B (At Least 1 Risk Factor, Not Including Diabetes; No TOD/CCD)	Risk Group C (TOD/CCD and/or Diabetes, With or Without Other Risk Factors)
High-normal (130-139/85-89)	Lifestyle modification	Lifestyle modification	Drug therapy§
Stage 1 (140-159/90-99)	Lifestyle modification (upto 12 mo)	Lifestyle modification‡ (up to 6 mo)	Drug therapy
Stages 2 and 3 (≥160/≥ 100)	Drug therapy	Drug therapy	Drug therapy

*Note: For example, a patient with diabetes and a blood pressure of 142/94 mm Hg plus left ventricular hypertrophy should be classified as having stage 1 hypertension with target organ disease (left ventricular hypertropy) and with another major risk factor (diabetes). This patient would be categorized as "Stage 1, Risk Group C," and recommended for immediate initiation of pharmacologic treatment. Lifestyle modification should be adjunctive therapy for all patients recommended for pharmacologic therapy.

† TOD/CCD indicates target organ disease/clinical cardiovascular disease

‡ For patients with multiple risk factors, clinicians should consider drugs as initial therapy plus lifestyle modifications

§ For those with heart failure, renal insufficiency, or diabetes.

3. Maintenance of drug therapy: (Table 7)

Table 7. General Guidelines to Improve Patient Adherence to Antihypertensive Therapy

Be aware of the problem and be alert to signs of patient nonadherence
Establish the goal of therapy: to reduce blood pressure to near normotensive levels with minimal side effects.
Educate the patient about the disease and its treatment
  Involve the patient in decision making
  Encourage family support
Maintain contact with the patient
  Encourage visits and calls to allied health personnel
  Allow the pharmacist to monitor therapy
  Give feedback to the patient via home BP readings
  Make contact with patients who do not return
Keep care inexpensive and simple
  Do the least workup needed to rule out secondary causes
  Obtain follow-up laboratory data only yearly unless indicated more often
  Use home blood pressure readings
  Use nondrug, low-cost therapies
  Use once-daily doses of long-acting drugs
  Use generic drugs and break larger doses of tablets in half
  If appropriate, use combination tablets
  Tailor medication to daily routines
Prescribe according to pharmacologic principles
  Add one drug at a time
  Start with small doses, aiming for 5- to 10-mm Hg reductions at each step
  Have medication taken immediately on awakening in the morning or after 4 a.m. if patient awakens to void
  Prevent volume overload with adequate diuretic and sodium restriction
Be willing to stop unsuccessful therapy and try a different approach
Anticipate side effects
Adjust therapy to ameliorate side effects that do not spontaneously disappear
Continue to add effective and tolerated drugs, stepwise, in sufficient doses to achieve the goal of therapy.

The overall game plan provided in JNC-6 (Figure 7) is currently appropriate, indicating three paths toward the choice of initial drug therapy: one for those with uncomplicated hypertension based on multiple randomized control trials; one for those with certain conditions in which "compelling" evidence exists for specific drugs; the third for various situations wherein certain drugs are known to provide additional benefit but have not been shown to reduce mortality (Table 8).

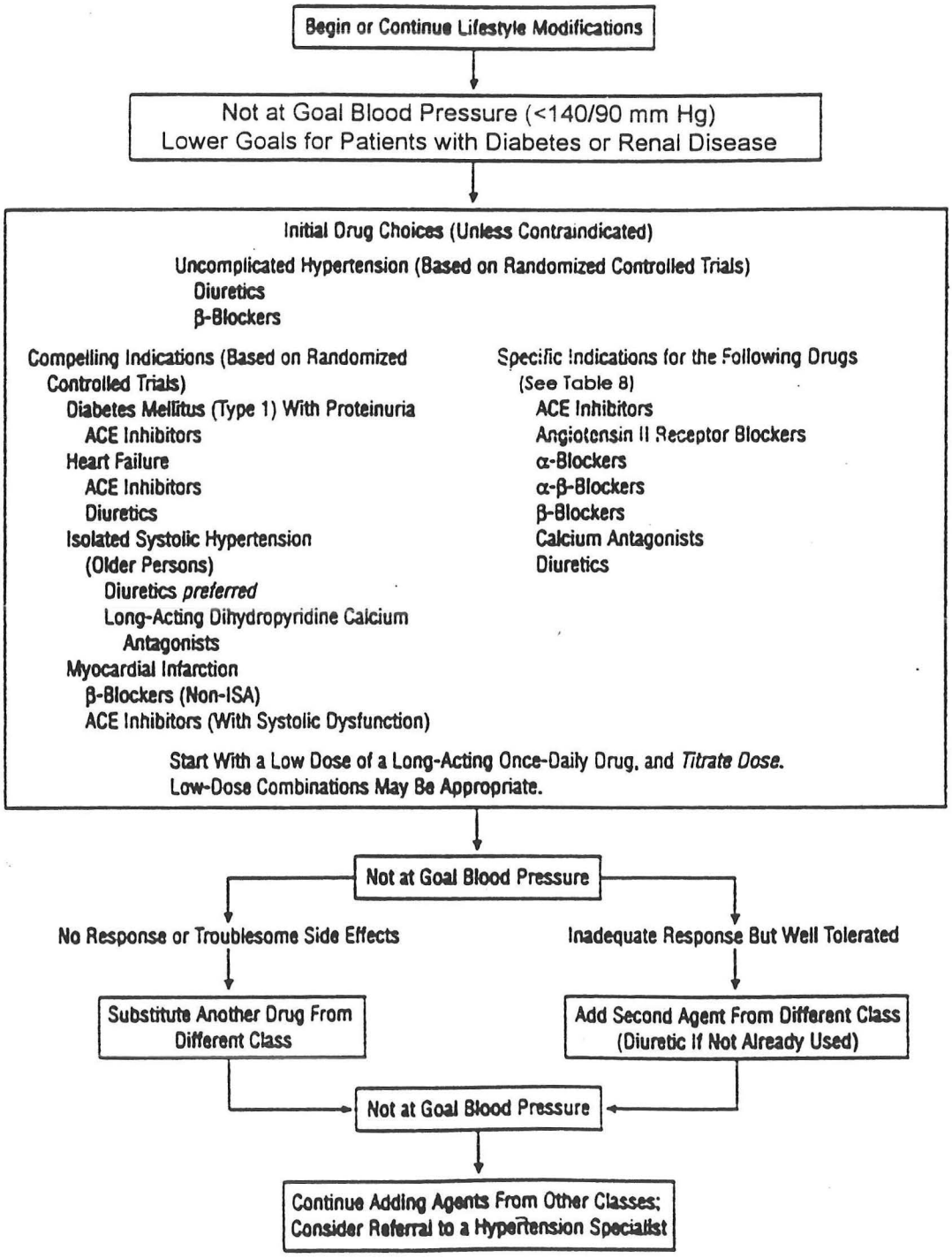

Figure 7.

Table 8. Considerations for Individualizing Antihypertensive Drug Therapy*

Angina	β-Blockers, CA
Atrial tachycardia and fibrillation	β-Blockers, CA (non-DHP)
Cyclosporine-induced hypertension	CA
Diabetes mellitus (types 1 and 2) with proteinuria	ACE 1 (preferred), CA
Diabetes mellitus (type 2)	Low-dose diuretics
Dyslipidemia	α-Blockers
Essential tremor	β-Blockers (non-CS)
Heart failure	Carvedilol, losartan
Hyperthyroidism	β-Blockers
Migraine	β-Blockers (non-CS), CA (non-DHP)
Myocardial infarction	Diltiazem, verapamil
Osteoporosis	Thiazides
Preoperative hypertension	β-Blockers
Prostatism (BPH)	α-Blockers
Renal insufficiency (caution in renovascular hypertension and creatinine level ≥3 mg/dL)	ACE 1

* CA, calcium antagonists; ACEI, angiotensin converting enzyme inhibitors; CS, cardioselective; non-DHP, non-dihydropyridine

The evidence for diuretics and beta-blockers for uncomplicated hypertensives below age 65 comes from twelve randomized, placebo-controlled trials (Mulrow et al., 1994) (Figure 8). These trials all used diuretics, in most as the only initial drug, and an adrenergic inhibitor as second.

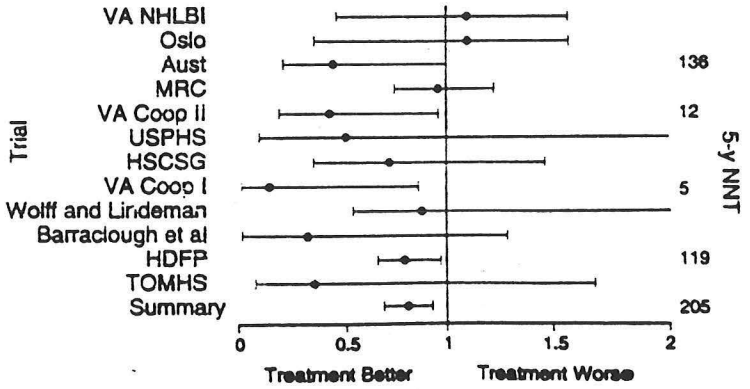

Figure 8. Quantitative analyses of cardiovascular outcomes in trials involving younger and middle-aged adults. VA NHLBI, VA/National Heart, Lung, and Blood Institute Study Group for Evaluating Treatment of Mild Hypertension; Oslo, Oslo Hypertension Study; Aust, Australian National Blood Pressure study; MRC, Medical Research Council trail; USPHS, U.S. Public Health Service; HSCSG, Hypertension-Stroke Cooperative Study Group; TOMHS, Treatment of Mild Hypertension Study. (Source: Mulrow et al., 1994).

The evidence for the drugs listed as "compelling" comes from multiple trials. The need for ACE inhibitors in diabetic nephropathy, CHF and post-MI and for beta-blockers post-MI is well recognized. The indication for diuretics as the preferred choice in elderly hypertensives with systolic hypertension comes mainly from three large randomized controlled trials wherein 12.5 to 15 mg of diuretic was the initial drug: SHEP, STOP-HTN, and MRC (Table 9).

The addition of long-acting dihydropyridine calcium antagonists is based on the Syst-Eur trial in which nitrendipine provided a 42% reduction in stroke and a 26% reduction in coronary events (Staessen et al., 1997) (Table 9). Since nitredipine is not marketed in the U.S., JNC-VI recommends any of the long-acting DHP calcium antagonists that are available.

Table 9. Effects of Therapy in Elderly Hypertensive Patients

	SHEP (1991)	STOP-HTN (Dahlöf, 1991)	MRC (1992)	SYST-EUR (1997)
Mean BP at entry	170/77	195/102	185/91	174/85
Relative difference in rate between treated and placebo groups				
Stroke	-33*	-47*	-25*	-42*
CAD	-27*	-13+	-19	-30
CHF	-55*	-51*		-29
All CVD	-32*	-40*	-17*	-31*

*Statistically significant
+ Myocardial infarction; sudden deaths reduced from 13 to 4

When all of the RCTs in both younger and older patients are combined, there is clearly greater cardiovascular protection from low doses of diuretics compared to either high doses of diuretics or beta-blockers (Psaty et al., 1997).

IMPROVING THE MANAGEMENT OF INDIVIDUAL PATIENTS

Case Report:

This 58 year old Caucasian man was initially diagnosed as hypertensive 8 years before (blood pressure = 160/100). He was treated with diuretic (Maxzide 25/37.5) and then atenolol (50 mg qAM) was added. Over the past year, his office blood pressure has risen (180-200/100-110) despite increased dose of atenolol (100 mg qAM), substitution of furosemide (40 mg qAM) for Maxzide and addition of first, clonidine 0.3 mg hs; then, verapamil SR (240 qAM) and, most recently, enalapril, 20mg qAM. He has occasional bitemporal headaches for which he takes ibuprofen but no other symptoms. He smokes one pack per day; drinks 2-3 beers most nights; has gained 15 pounds over the past year (current weight = 195, height =5'10"), which he attributes to less physical activity since spraining his ankle while bowling.

Physical exam: blood pressure = 190/110, P = 48. Generalized obesity; fundi: arteriolar narrowing and A-V nicking; no cervical or abdominal bruits; heart, lungs negative; femoral pulses weak but palpable. No edema.

Lab data: HCT = 43%; UA = 1+ protein; serum Na/K = 138/3.1; creatinine = 1.3; glucose = 98 ECG: borderline LVH.

The inadequate control of this patients' hypertension could reflect multiple causes (Table 10).

Table 10. Causes for inadequate Responsiveness to Therapy

Pseudo-resistance
- White coat or office elevations
- Pseudohypertension in the elderly

Nonadherence to therapy
- Side effects or costs of medication
- Lack of consistent and continuous primary care
- Inconvenient and chaotic dosing schedules
- Instructions not understood
- Organic brain syndrome (e.g., memory deficit)

Drug-related causes
- Doses too low
- Inappropriate combinations
- Rapid inactivation (e.g., hydralazine)
- Drug actions and interactions
  - NSAIDS
  - Sympathominetics
    - Nasal decongestants
    - Appetite suppressants
    - Cocaine and other street drugs
    - Caffeine
  - Oral contraceptives
  - Adrenal steroids
  - Licorice (as may be found in chewing tobacco)
  - Cyclosporine, tacrolimus
  - Erythropoietin

Associated conditions
- Smoking
- Increasing obesity
- Sleep apnea
- Insulin resistance or hyperinsulinemia
- Ethanol intake more than 1 ounce a day
- Anxiety-induced hyperventilation or panic attacks
- Chronic pain
- Intense vasoconstriction (Raynaud phenomenon, arteritis)

Identifiable causes of hypertension

Volume overload
- Excess sodium intake
- Progressive renal damage (nephrosclerosis)
- Fluid retention from reduction of blood pressure
- Inadequate diuretic therapy

Pseudoresistance

Although the "white-coat" effect has been said to be responsible for almost half of apparently resistant hypertension (Waeber et al., 1987; Mezzetti et al., 1997), most treated hypertensives with persistently high office readings also have high out-of-office readings (Mancia et al., 1997) (Figure 9), so that inadequate control is likely not commonly attributable only to the white-coat effect.

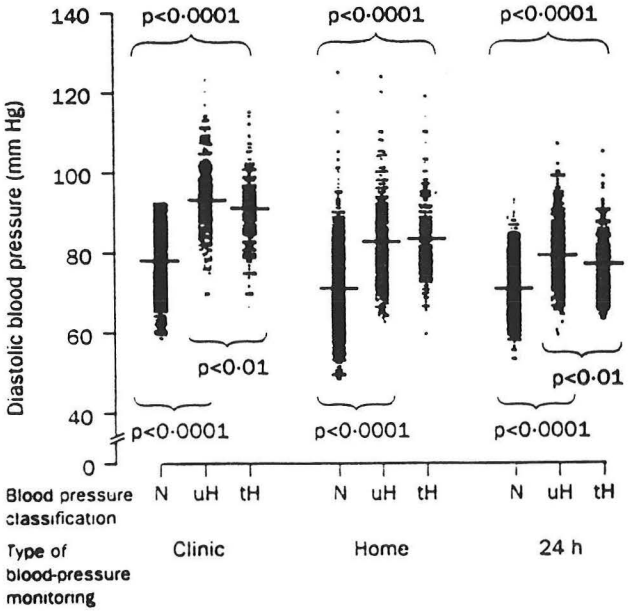

Figure 9. Individual systolic and diastolic blood pressure values in normotensive, untreated hypertensive, and treated hypertensive participants taken in the clinic, at home and with 24 hour ambulatory monitoring (Source: Mancia et al., 1997)

Nonetheless, this patient should be asked to monitor his home BP with an inexpensive semi-automatic device such as the AND UA702 model, which was top-rated in the October 1996, Consumer Report, available for $40 - 50 with a large cuff. Until his BP is better controlled, he should take frequent readings. Once control is established, an occasional reading should be obtained soon after arising from sleep to ensure adequate control of the early morning surge in BP that is responsible for the increase in cardiovascular complications at that time.

Non-adherence to therapy:

This may be the most common cause of resistant hypertension at Parkland and other hospitals where large numbers of indigent patients are seen because of many impediments to adherence, in particular access to coordinated care provided by a continuously available provider. The various maneuvers listed in Table 7 should help prevent or overcome nonadherence to therapy. Among the most important is once-a-day dosing of initially low doses of antihypertensive drugs.

Volume overload:

In most series, the most common cause of resistance is volume overload secondary to inadequate diuretic, in particular the widespread use of once-a-day furosemide (Yakovlevitch and Black, 1991). According to the National Ambulatory Medical Care Survey, there were over 23 million prescriptions written in 1996 for furosemide versus 17 million for HCTZ (Woodwell, 1997). As shown years ago (Wilcox et al., 1983), once-a-day (and likely twice-a-day) furosemide will not maintain the slight contraction of intravascular volume that is needed to lower BP as long as access to sodium is allowed during the many hours without diuretic action (Figure 10). The need for such continual diuretic action is accentuated by the tendency for reactive renal sodium retention when BP is lowered, resulting from the rightward shift in the pressure-natriuresis relation that is inherent to the development of hypertension (Figure 11).

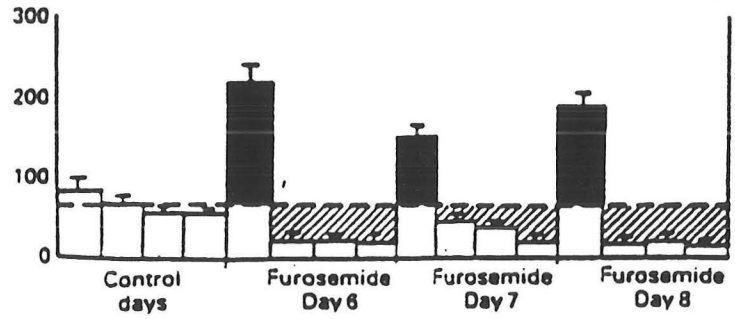

Figure 10. Inadequate Diuretic: Once-A-Day Furosemide. Values for 6 hourly rates of sodium excretion for the control days and the 3 days when furosemide was given. The dashed horizontal lines represents the average rate of Na+ excretion determined during the control days, and the solid and diagonal shading represent the differences between the measured Na+ excretion and this basal rate of excretion (Source: Wilcox CS et al., 1983).

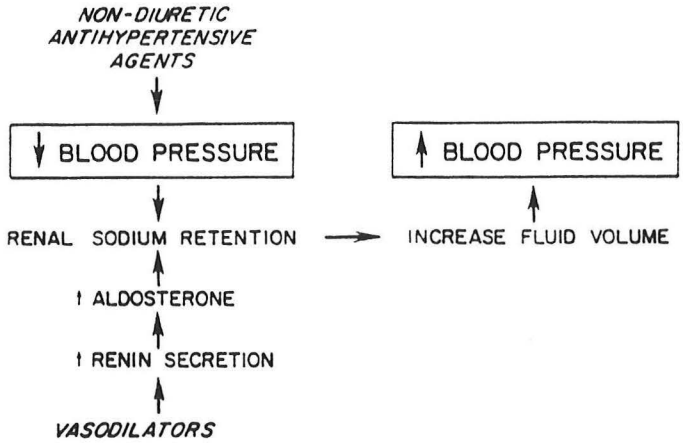

Figure 11. Manner by which nondiuretic antihypertensive agents may lose their effectiveness by reactive renal sodium retention (Source: Kaplan, 1998).

The problem is further exacerbated by the usual high sodium intake and moderate renal insufficiency common to more severe hypertension. The solution is to give adequate doses of long-acting diuretic. For those with serum creatinine below 2 mg/dl, a morning dose of HCTZ is likely adequate, although the amount may need to be greater than the 12.5 mg that is enough for most uncomplicated hypertension (Brater, 1988). For those with serum creatinine above 2 mg/dl, daily therapy with either two or three doses of furosemide, or one or two doses of torsemide (Demadex) (Dunn et al., 1995) or one dose of metolazone (Zaroxolyn) (Paton and Kane, 1977) may be used.

Drug-related causes:

Of these the interaction with non-steroidal anti-inflammatory drugs (NSAIDs) may be most common. NSAIDs may blunt the effect of all antihypertensive drugs with the apparent exception of calcium antagonists (de Leeuw, 1996; Johnson, 1997). Acetaminophen is a suitable alternative which will not interfere with antihypertensives.

Sympathomimetics may raise BP. The effect of caffeine is usually not persistent because of the rapid development of tolerance to its sympathomimetic effect (James, 1997). However, most over-the-counter diet pills that contain pseudoephrine or phenylpropanolamine may raise BP (Lake et al., 1990); caution is advised for the recently approved sibutramine, but it does not appear to raise BP.

The drug-related factors in this case mainly involve too-small doses of too-short acting agents including furosemide, atenolol, clonidine, verapamil SR, and enalapril.

This patient has multiple associated conditions which could make his hypertension resistant, including smoking, increasing obesity (often with sleep apnea, always with insulin resistance), physical inactivity and perhaps excessive alcohol intake.

The contribution of smoking may easily be missed if office BPs are taken thirty minutes or longer after the last cigarette (see Figure 5). Increasing obesity may interfere with BP control in multiple ways and control may be almost impossible until some weight loss is accomplished. This patient's current intake of 2-3 beers per day should not pose a problem other than for the extra calories (Shaper et al., 1988) (Figure 12). However, some people are more sensitive to the pressor effect of alcohol so that a lesser daily intake should be recommended, thereby also to reduce his caloric intake.

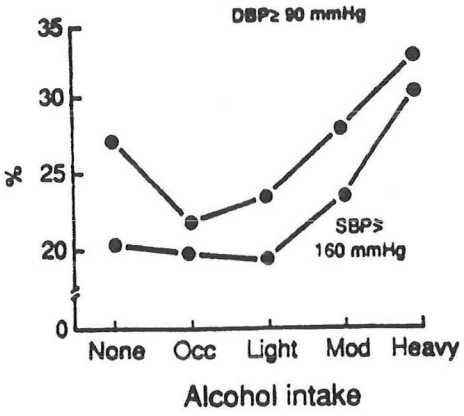

Figure 12. Age-adjusted prevalence rates (in percent) of measured systolic and diastolic hypertension by levels of alcohol intake in drinks. Occ, occasional; light, one to two daily; Mod. Moderate, three to six daily; heavy, more than six daily (Source: Shaper et al., 1988).

Identifiable causes of hypertension:

Renal parenchymal disease is the most common of these and is ascertained simply by the presence of an elevated serum creatinine. Renal vascular disease is the most likely of these to be unrecognized and, when looked for, has been identified in up to 20% of resistant hypertensives (Horvath et al., 1982; Emovon et al., 1996). In patients with accelerated-malignant hypertension or severe hypertension with progressive renal insufficiency, a renovascular cause may be found in up to 40% (Davis et al., 1979; Greco and Breyer, 1997) so that renal angiography should be obtained in all such high-likelihood patients (Mann and Pickering, 1992).

Obviously, a large number of other identifiable causes of increasing hypertension may be present but most are obvious by history, physical exam and screening laboratory tests.

If this patient's hypertension remains uncontrolled after appropriate changes in his regimen (Table 11), a search for renovascular disease should be considered. Hopefully, he will respond to a new regimen that will correct most of the reasons for his currently inadequately controlled hypertension.

Table 11. Current and New Regimen

Old Regimen	New Regimen
Ad lib diet, 2-3 beers/d	1800 calorie, 2 g sodium; 1 beer/day
No physical activity	Daily aerobic exercise
Ibuprofen prn	Acetaminophen prn
Furosemide, 40 qAM	HCTZ 25 mg qAM (+ triamterene)
Atenolol, 100 qAM	Metroprolol XL 50 qAM
Clonidine, 0.3 qh.s.	Slowly discontinue
Verapamil SR, 240 qAM	Felodipine, 10 qAM or Amlodipine, 10 qAM
Enalapril, 20 mg qAM	Quinapril, 20 qAM or Trandolapril, 2 qAM

Most hypertensives can have their condition controlled by appropriate use of lifestyle modifications and antihypertensive drugs. The current failure to adequately control almost 75% of U.S. hypertensives, despite the efforts being made to do so, strongly supports the need for population-wide strategies. We can do better.

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