INTERNAL MEDICINE GRAND ROUNDS

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Two Hypertensive Patients with Problems Involving Detection, Evaluation, and Treatment

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Dr. Kaplan's interest is in clinical hypertension. He has served as a consultant to most companies that market non-drug and drug therapies for hypertension. In this capacity, he has received funding for research, seminars, and travel.

He does not recommend non-approved uses of either non-drugs or drugs and he attempts to remain unbiased (except about once-a-day furosemide and clonidine).

I. INTRODUCTION

Hypertension is common and poorly controlled. It will become much more common; hopefully, it can be better controlled.

Two major reasons explain the increasing incidence of hypertension: increasing life expectancy and expanding prevalence of obesity among people in all developed and developing societies. The increase in hypertension with aging is largely caused by rigidity or stiffness of the large capacitance arteries from atherosclerosis. The increase with obesity is due to multiple effects that impair endothelial function in addition to additional complications from the type 2 diabetes that so often accompanies hypertension and obesity.

Recent publications from the Framingham Study portray the problem of aging (Vasan et al., 2001a; Vasan et al., 2002) (Figure 1) whereas data from the Nurses Health Study document the major impact of even small amounts of weight gain (Willett et al., 1999) (Figure 2).

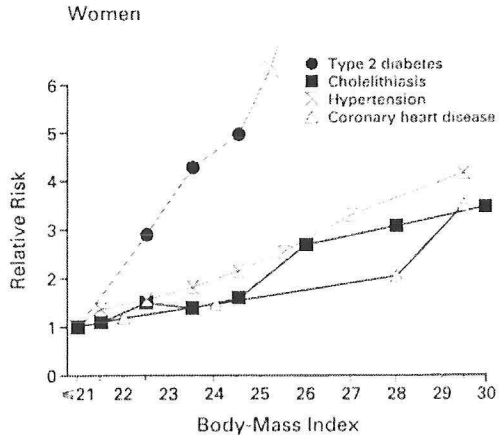
FIGURE 1

Lifetime Risk of Developing Hypertension in Framingham Subjects Normotensive At Age 55 or 65

	Percent Developing Hypertension			
Interval (years)	Women		Men	
Age	55	65	55	65
10	52	64	56	72
15	72	81	78	85
20	83	89	88	90

(From Vasan et al. JAMA 2002;287:1003.)

FIGURE 2



RELATION BETWEEN BODY-MASS INDEX UP TO 30 AND THE RELATIVE RISK OF TYPE 2 DIABETES, HYPERTENSION, CORONARY HEART DISEASE, AND CHOLELITHIASIS. *Figure 2 shows these relations for women in the Nurses' Health Study, initially 30 to 55 years of age, who were followed for up to 18 years. (From Willett et al. NEJM 1999;341:430.)*

The weight gain, particularly if deposited as visceral or abdominal fat, leads to the metabolic syndrome (Table 1). The prevalence of abdominal obesity within adults in the U.S. is alarming, well above 60% in people over age 50 (Okusun et al., 1999).

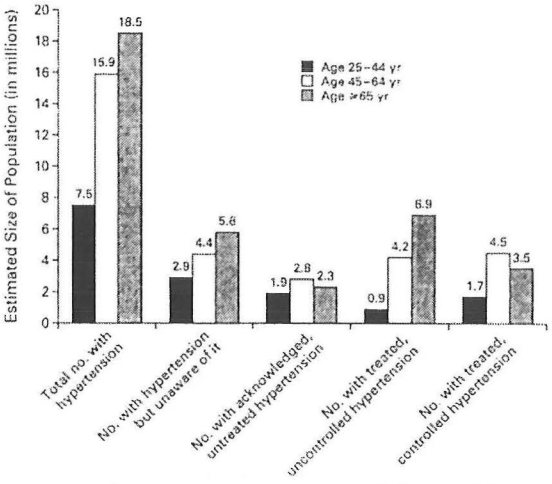
Table 1. The Metabolic Syndrome

Risk Factor	Defining Level
Abdominal obesity (waist circumference)	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dL
High-density lipoprotein cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥110 mg/dL

Both atherosclerotic rigidity and obesity are preventable but prospects for prevention seem slim. Nonetheless, aggressive legal and educational measures have diminished cigarette smoking, at least in the U.S., so some optimism may be warranted.

Meanwhile, better management of hypertension is needed since surveys continue to document the inadequacy of current management, even in teaching hospitals, in large part because of physician non-compliance with established guidelines (Hyman et al., 2001; Oliveria et al., 2002) (Figure 3).

FIGURE 3



Number of persons classified in the various categories of hypertension in each age group among the members of the U.S. population who were at least 25 years old. (From Hyman et al. NEJM 2001;345:481.)

Two patients recently seen portray some of the problems that need to be addressed.

II. DETECTION AND EVALUATION OF HYPERTENSION

Patient MR: This 32 year old woman was apparently normotensive until week 32 of her first pregnancy 2 years before when preeclampsia was recognized. She was hospitalized, given multiple therapies, and delivery was induced one week later. Her baby girl weight only 3 lbs. but has done well since.

Post-partum, her office blood pressures remained elevated, averaging 160/95. Six weeks post-partum, she was started on a dihydropyridine calcium channel blocker (CCB), nifedipine GITS, 30 mg q a.m. Because her blood pressure didn't respond well, the daily dose was increased to 60 mg and then 90 mg.

During the last 6 months, increasingly frequent episodes of band-like headache, dizziness, fast and hard heart beats ("feeling as if my heart was going to jump out of my chest"), and flushing have occurred.

In addition to routine lab tests, which were all normal, a 24-hour urine metanephrine assay revealed a slightly elevated level (620 μg/24 hours).

A. History

Table 2. Important Aspects of the History

Duration of the hypertension		Presence of other risk factors	
Last known normal blood pressure		Smoking	Diabetes
Course of the blood pressure		Dyslipidemia	Physical inactivity
Prior treatment of the hypertension		Concomitant diseases	
Drugs: types, doses, side effects		Dietary history	
Intake of agents that may interfere		Weight change	
Non-steroidal antiinflammatory (NSAIDs)		Fresh vs processed foods	
Oral contraceptives		Sodium	
Sympathomimetics		Saturated fats	
Adrenal steroids		Sexual function	
Excessive sodium intake		Features of sleep apnea	
Alcohol (> 2 drinks/day)		Early morning headaches	
Herbal remedies		Daytime somnolence	
Family history		Loud snoring	
Hypertension		Erratic sleep	
Premature cardiovascular disease or death		Symptoms of anxiety-induced hyperventilation	
Familial diseases: pheochromocytoma, renal disease, diabetes, gout		Paresthesias	
		Palpitations	
Symptoms of secondary causes		Chest discomfort	
Muscle weakness		Dizziness	
Spells of tachycardia, sweating, tremor		Fatigue, etc.	
Thinning of the skin		Ability to modify lifestyle and maintain therapy	
Flank pain		Understanding the nature of hypertension and the need for regimen	
Symptoms of target organ damage		Ability to perform physical activity	
Headaches	Dyspnea	Source of food preparation	
Transient weakness or blindness	Edema	Financial constraints	
Loss of visual acuity	Claudication	Ability to read instructions	
Chest pain		Need for care providers	

Specific items that should be noted in this young woman include: use of oral contraceptives, family history, presence of other cardiovascular risk factors, weight change, and both causes and additional symptoms of anxiety.

This patient was not taking oral contraceptives. Her mother had hypertension and suffered a disabling stroke at age 58. The patient smokes ½ pack per day and has gained about 15 lbs. over the past 2 years. She denies paresthesias but feels short of breath ("Can't seem to get enough air in") and chronically fatigued.

B. Physical Exam (Table 3)

Table 3. Important Aspects of the Physical Examination

Accurate measurement of blood pressure
General appearance: distribution of body fat, skin lesions, muscle strength, alertness
Fundoscopy
Neck: palpation and auscultation of carotids, thyroid
Heart: size, rhythm, sounds
Lungs: rhonchi, rales
Abdomen: renal masses, bruits over aorta or renal arteries, femoral pulses, waist circumference
Extremities: peripheral pulses, edema
Neurologic assessment, including cognitive function

The items listed are those contained in a routine exam but directed specifically toward hypertension. In a young woman, careful listening for an abdominal bruit as evidence of renovascular hypertension from medial fibroplasia of the renal arteries may be the most important.

This patient had no abnormalities on her physical exam.

C. Laboratory Testing

These are needed for all newly recognized hypertensives: hematocrit, urine analysis, blood electrolytes, creatinine, glucose and lipid profile, and an electrocardiogram. Additional studies should only be done if there are suggestive features of an identifiable cause that can be reversed (Table 4).

Table 4. Overall Guide to Workup for Identifiable Causes of Hypertension

	Diagnostic Procedure	
Diagnosis	**Initial**	**Additional**
Chronic renal disease	Urinalysis, serum creatinine, renal sonography	Isotopic renogram, renal biopsy
Renovascular disease	Captopril-enhanced isotopic renogram, duplex sonography	MR or CT angiogram, aortogram
Coarctation	Blood pressure in legs	Echocardiogram, aortogram
Primary aldosteronism	Plasma and urinary potassium, plasma renin and aldosterone	Plasma or urinary aldosterone after saline load, adrenal CT, and adrenal venous sampling
Cushing's syndrome	Morning plasma cortisol after 1 mg dexamethasone at bedtime	Urinary cortisol after variable doses of dexamethasone, adrenal CT and scintiscans
Pheochromocytoma	Plasma metanephrine Spot urine for metanephrine	Urinary catechols; plasma catechols (basal and after 0.3 mg clonidine); adrenal CT and scintiscans

This patient had recently had all of the routine tests except for the ECG. All were normal.

D. Confirmation of Hypertension

Perhaps even before going through the history, physical exam and laboratory testing, the presence of sustained hypertension should be confirmed. Recall that 80% of people have a higher blood pressure in the office than outside, i.e.

white-coat effect, and 20 to 30% have normal out of the office BP despite repeated office readings >140/90 mm Hg, i.e. white-coat or isolated office hypertension (Kaplan, 2002).

The problem was nicely delineated by Hall et al. (1990) (Table 5). These data document the significantly lower average of the 32 home readings per patient taken during the 2 weeks between the first and second clinic visits in 268 patients having a BP above 160/95 mm Hg on three prior occasions before the first clinic reading. The home readings were lower in 80% of the patients, by more than 20/10 mm Hg in 40%, so that therapy was deemed unnecessary in 38% of untreated patients and reducible in 16% of treated patients. The accuracy of the home readings taken with the electronic devices is evident by the identical readings taken with that device and the mercury sphygmomanometer at the second clinic visit.

Table 5. Blood Pressure Recorded at Home Between Clinic Visits

	First Clinic Reading (Mercury Manometer)		2-Week Home Series (Electronic Device)		Second Clinic Reading			
					Electronic Device		Mercury Manometer	
Patient Group	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
Untreated (n = 114)	174	103	148	90	165	95	164	97
Treated (n = 154)	177	104	147	87	163	95	164	95

(Data from Hall C et al. J Hum Hypertens 1990;4:501-507.)

Multiple self-taken readings with an inexpensive semi-automatic electronic device can document the usual range of BP. Caution is needed to ensure that readings are obtained at varying times and particularly when the patient is under stress to ensure an accurate profile.

In the near future, automatic ambulatory BP monitoring (ABPM) will be much more widely used since third-parties are now providing compensation for the procedure if performed under rather strict and narrow conditions. Only with ABPM can nighttime readings be obtained and these have been recognized to serve a prognostic purpose (Kario et al., 2002; Verdecchia, 2000). In particular, the failure of the BP to dip during sleep is associated with a worse prognosis.

As for this patient, on the basis of the office readings initially available, the likelihood of sustained hypertension is about 50% (Perry and Miller, 1992). She took about 30 readings over the next few weeks. They averaged 150/90 so she had documented hypertension, particularly since she was continuing to take nifedipine.

E. Elucidation of Symptoms

Hypertension, before it is recognized, is rarely symptomatic. However, many hypertensives have symptoms which they ascribe to their elevated BP (Kjellgren et al., 1998). Most of these symptoms are common to the functional somatic syndromes frequently found in people mistakenly diagnosed as having an organic disease (Barsky and Borus, 1999; Wessely et al., 1999) (Table 6).

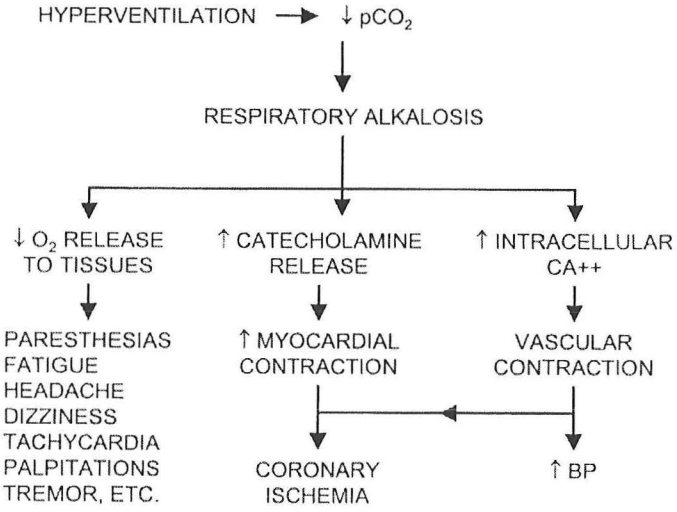
Table 6. Functional Somatic Syndromes by Specialty

Gastroenterology	Irritable bowel syndrome, non-ulcer dyspepsia
Gynaecology	Premenstrual syndrome, chronic pelvic pain
Rheumatology	Fibromyalgia
Cardiology	Atypical or non-cardiac chest pain
Respiratory medicine	Hyperventilation syndrome
Infectious diseases	Chronic (postviral) fatigue syndrome
Neurology	Tension headache
Dentistry	Temporomandibular joint dysfunction, atypical facial pain
Ear, nose, and throat	Globus syndrome
Allergy	Multiple chemical sensitivity

Reprinted with permission from Wesseley et al. Functional somatic syndromes: One or many? *Lancet* 1999;354:936-939.

These symptoms often reflect the anxiety of having "the silent killer," particularly if it is not under good control and even more so if, as in this patient, there is a family history of serious sequelae from hypertension. Such anxiety is often manifested by recurrent acute hyperventilation or, in many, overt panic attacks (Davies et al., 1999). Most of the symptoms described by anxious hypertensives such as this patient—bandlike headaches, dizziness, palpitations, dyspnea, and chronic fatigue—may reflect recurrent hyperventilation as noted in one-third of 300 patients referred to me for difficult to manage hypertension (Kaplan, 1997) (Figure 4).

FIGURE 4



The mechanisms by which acute hyperventilation may induce various symptoms, coronary ischemia, and a rise in blood pressure.

This patient developed her typical symptoms after 40 seconds of voluntary hyperventilation. By the end of this period, her pulse had risen from 84 to 102 and her BP from 140/85 to 160/95.

The syndrome was explained to the patient and she was shown how to rebreathe into a #6 paper sack as often as needed and as soon as the first symptom appears. Counseling was advised with a clinical psychologist. A patient instruction sheet which I have found useful is provided as Appendix 1.

F. Management of Hypertension

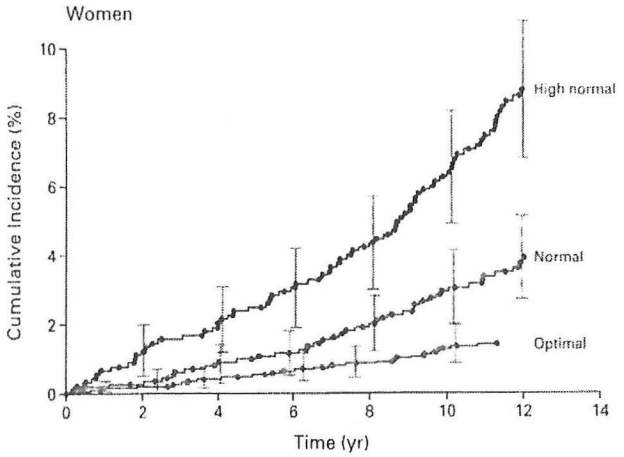
1. Lifestyle Modifications

All patients, even with only BP considered "normal," should be asked to modify unhealthy lifestyles (Table 7). Those with high-normal BP levels, between 130-139/85-89, have a significantly greater risk for cardiovascular events than do those with lower levels (Vasan et al., 2001b) (Figure 5) so that patients should not wait until hypertension becomes overt to modify lifestyles.

Table 7. Lifestyle Modifications

- Lose weight if overweight
- Limit alcohol intake
- Increase aerobic physical activity (30-45 minutes most days of the week)
- Reduce sodium intake to no more than 100 mmol/day (2.4 g of sodium or 6 g of sodium chloride)
- Maintain adequate intake of dietary calcium and magnesium
- Stop smoking and reduce intake of dietary saturated fat and cholesterol

FIGURE 5



Cumulative Incidence of Cardiovascular Events in Women without Hypertension, According to Blood-Pressure Category at the Base-Line Examination in the Framingham cohort.

Vertical bars indicate 95 percent confidence intervals. Optimal blood pressure is a systolic pressure of less than 120 mm Hg and a diastolic pressure of less than 80 mmHg. Normal blood pressure is a systolic pressure of 120 to 129 mm Hg or a diastolic pressure of 80 to 84 mm Hg. High-normal blood pressure is a systolic pressure of 130 to 139 mm Hg or a diastolic pressure of 85 to 89 mm Hg. If the systolic and diastolic pressure readings for a subject were in different categories, the higher of the two categories was used. (From Vasan et al. NEJM 2001;345:1291-1297.

Unhealthy lifestyles are easier to prevent than to overcome. The critical need is to increase physical activity, particularly in children and adolescents, the group with the most rapidly growing relative rate of obesity in the U.S. and other developed societies (Chinn and Rona, 2001). Simply turning off children's TVs and computers will help (Robinson, 1999). For adults, just walking 30 minutes a day and losing a few pounds can prevent hypertension and diabetes (Diabetes Prevention, 2002) and weight gain can be prevented by more brisk activities such as walking up stairs instead of taking the elevator (Blumenthal et al., 2000).

Many of the list of lifestyle changes affect the perceived quality of life. Fortunately, coffee is safe (Klag et al., 2002) and moderate daily consumption of alcohol provides no risk of hypertension (Thadhani et al., 2002) while offering protection from heart attack, stroke, and dementia (Ruitenberg et al., 2002), likely related to a slowing of arterial stiffness (Hougaku et al., 2001) and a rise in HDL-cholesterol levels. In most studies, including Ruitenberg et al.'s, red wine was no better than white wine, beer, or liquor and, in fact, beer may be best.

This patient had gained about 15 lbs. since delivery and did not perform physical activity beyond "chasing after my baby." She needs to lose weight since small amounts of excess weight can increase BP as seen in Figure 2. Moreover, she should perform regular physical activity daily. Her BP will likely fall and exercise may relieve some of the manifestations of her stress and anxiety.

2. Antihypertensive Drug Therapy

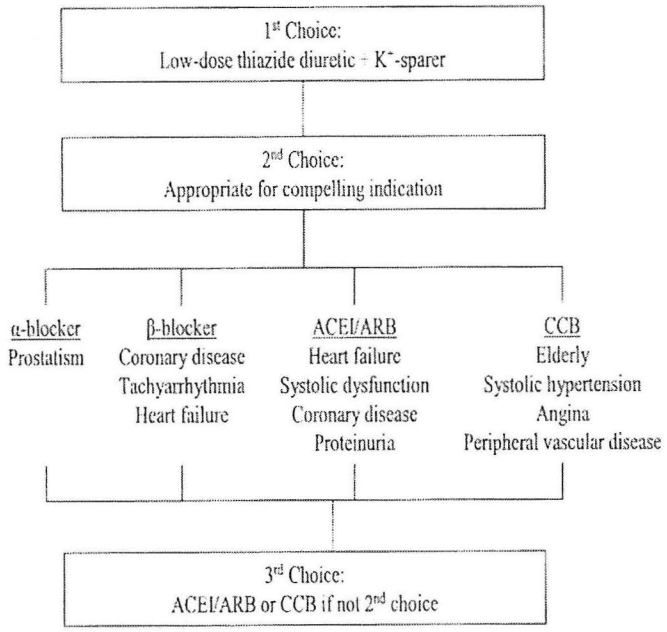
If, despite lifestyle changes, out-of-office BPs are above 140/90, antihypertensive drugs should be considered. While the patient seems to be tolerating a fairly large dose of a DHP-CCB (although it could contribute to her headaches and flushing), therapy should start on the foundation of a low-dose thiazide diuretic (12.5 mg HCT q a.m.) with a potassium-sparer. Spironolactone is an attractive alternative to triamterene; the combination of HCT + spironolactone, 25 + 25 mg, is inexpensive; one-half tablet should be enough for many.

If control is not achieved, a second drug should be added. Since she has no compelling indication for a specific choice (Table 8), any member of the 4 other major classes would be appropriate (Figure 6). In younger people (who tend to have higher levels of renin-angiotensin), a renin-inhibiting drug may be more effective (Dickerson et al., 1999), whereas in an older or black patients (who have lower levels of renin), either a diuretic or a CCB will likely be more effective (Morgan et al., 2001).

Table 8. Compelling Indications for Antihypertensive Drugs

Indication	Drug	Indication	Drug
Elderly with ISH	Diuretic, CCB-DHP	Cerebrovascular disease	Diuretic ± ACEI
Black	Diuretic, CCB	Nephropathy	
		Type I DM	ACEI
Heart Disease		Type 2 DM	ARB
Post-MI	ACEI, β-blocker	Non-diabetic	ACEI
LV dysfunction	ACEI		
CHF	ACEI, β-blocker, spironolactone	Prostatism	α-blocker
LVH	ARB		

FIGURE 6



A rational treatment algorithm.

New agents have an attraction that they may not deserve. This has been true for angiotensin II-receptor blockers (ARBs) which were being used increasingly without evidence from outcome studies. Now, fortunately, they have been shown to reduce progression of type 2 diabetic nephropathy compared to placebo in 3 randomized, controlled trials (Brenner et al., 2001; Lewis et al., 2001; Parving et al., 2001) and to protect hypertensive patients with LVH better than the beta-blocker atenolol in the LIFE trial (Lindholm et al., 2002). In this trial, HCT was also given to 60% of patients and often other drugs as well.

Nonetheless, before switching all now on an ACEI to an ARB, recall that only ACEIs have been tested in type 1 diabetic nephropathy and they clearly provide, as yet, unequaled benefit in CHF (Pitt et al., 2000) and, with a diuretic, in prevention of recurrent stroke (PROGRESS, 2001).

III. TREATMENT OF RESISTANT HYPERTENSION

Patient HB: This 58 year old man was found to be hypertensive on a routine insurance exam 20 years ago and has taken antihypertensive drugs ever since with a gradual escalation of therapy over the past 3 years.

Currently, he is taking:
- *Valsartan 160 mg q a.m.*
- *Quinapril 40 mg q a.m.*
- *Labetalol 100 mg bid*
- *Metoprolol 100 mg bid*
- *Clonidine 0.3 mg bid*
- *Furosemide 80 mg q a.m.*

Additional therapies:
- *ASA 80 mg q a.m.*
- *Vioxx® 25 mg prn*
- *Zolofi® 50 mg q a.m.*
- *Multivitamin caps 1 qd*

Despite this regimen, which he maintains is taken regularly, his office and home BPs usually are around 160/85 mm Hg. He feels fatigued even after sleep and is often drowsy during the day at his job as office manager of a car leasing company. He feels stressed and has recently noted inability to maintain an erection.

In the past, he had a captopril-enhanced isotopic renogram (normal), an exercise stress test (normal), an echocardiogram (significant LVH but normal ejection indices).

Despite repeated efforts to stop smoking, he continues to smoke 10-12 cigarettes a day. He usually has a martini before dinner, 1 to 2 glasses of wine during dinner, and cognac before bedtime. When he cut down smoking from 2 packs per day to one-half ppd, he gained about 15 lbs. and has been around 210 for the past year (Ht = 5'10"). He avoids highly salted food but does almost no physical activity.

Recent lab work reveals urine protein of 180 mg/24 hours; serum sodium = 138, potassium = 3.9, creatinine = 1.6, and glucose = 130. Plasma total cholesterol = 242, HDL = 42.

A. Need for Additional Diagnostic Studies

Among the multiple causes of resistant hypertension (Table 9), a number require special testing to identify. A few in particular have been recently claimed to be often unrecognized and in need of consideration in every patient with truly resistant hypertension. Emphasis will be given to those considered in patient HB.

Table 9. Causes for Inadequate Responsiveness to Therapy

Pseudo-resistance	Associated conditions
White coat or office elevations	Smoking
Pseudohypertension in the elderly	Increasing obesity
	Sleep apnea
Nonadherence to therapy	Insulin resistance or hyperinsulinemia
Side effects or costs of medication	Ethanol intake more than 1 ounce a day
Lack of consistent and continuous primary care	Anxiety-induced hyperventilations or panic attacks
Inconvenient and chaotic dosing schedules	Chronic pain
Instructions not understood	Intense vasoconstriction (Raynaud phenomenon, arthritis)
Organic brain syndrome (e.g. memory deficit)	
	Identifiable causes of hypertension
Drug-related causes	Renal parenchymal disease
Doses too low	Renovascular disease
Inappropriate combinations	Primary aldosteronism
Rapid inactivation (e.g. hydralazine)	Pheochromocytoma, etc.
Drug actions and interactions	
NSAIDS	Volume Overload
Sympathomimetics	Excess sodium intake
Nasal decongestants	Progressive renal damage (nephrosclerosis)
Appetite suppressants	Fluid retention from reduction of blood pressure
Cocaine and other street drugs	Inadequate diuretic therapy
Caffeine	
Oral contraceptives	
Adrenal steroids	
Licorice (as may be found in chewing tobacco)	
Cyclosporine, tacrolimus	
Erythropoietin	

From the Joint National Committee. The sixth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI). Arch Intern Med 1997;157:2413-2446.

1. Obstructive Sleep Apnea (OSA)

OSA has been found in almost one-third of hypertensives and about half of patients with OSA are hypertensive (Peppard et al., 2000). In particular, OSA has been frequently found in hypertensive patients resistant to multidrug therapy (Logan et al., 2001).

As in this patient, poor quality sleep and daytime drowsiness are usually seen. If his spouse notices loud snoring and interruptions of sleep with apnea during the night, the diagnosis is more likely and a proper sleep study should be obtained. This study is difficult to obtain for indigent patients but is more readily available among insured patients in the community.

If recognized, continuous positive airway pressure (CPAP) can provide remarkable relief of the symptoms and lower the daytime BP (Pepperell et al, 2002), if it can be tolerated by the patient. In addition, a dental appliance that prevents prolapse of the tongue has been reported to be effective (Walker-Engström et al., 2002).

If this patient's BP does not respond to a more rational therapeutic regimen and if his spouse confirms loud snoring and interrupted sleep, a sleep study should be obtained.

2. Renal Parenchymal Disease

As Johnson et al. (2002) have reviewed, subtle acquired renal injury may be responsible for sodium-sensitive hypertension that is common in obese, diabetic, elderly, and black patients. Microalbuminuria is often the earliest clinical feature but progressive renal insufficiency may follow.

Microalbuminuria, defined as urinary albumin-creatinine ratio of 30 to 299 mg/g, was found in 29% of diabetics, 16% of hypertensives, and 11.5% of the entire cross-section of the U.S. population (Jones et al., 2002). A dipstick test for microalbuminuria should be done on every hypertensive since it is an indicator of risk for LVH (Wachtell et al., 2002), accelerated progression of arterial stiffness (Benetos et al., 2002a), and inadequacy of antihypertensive therapy (Redon et al., 2002).

Patient MR has microalbuminuria and an elevated serum creatinine, indicating the need for additional renal protection.

3. Renovascular Disease

Of all the identifiable (secondary) forms of hypertension, renovascular disease is least obvious by routine history, physical exam, and routine lab testing. Clinical clues should be looked for (Table 10). Among 297 hypertensives undergoing cardiac angiography, renal artery stenoses of 50% or more were found in 19.2% (Rihal et al., 2002). However, such "drive-by" screening is not recommended unless there are clinical clues, thereby to avoid unnecessary therapy for non-significant renal artery disease (Zierler, 2002).

Table 10. Clinical Clues for Renovascular Hypertension

History	Laboratory
Onset of hypertension before age 30 or after age 50	Secondary aldosteronism
Abrupt onset of hypertension	Higher plasma renin
Severe or resistant hypertension	Low serum potassium
Symptoms of atherosclerotic disease elsewhere	Low serum sodium
Negative family history of hypertension	Proteinuria, usually moderate
Smoker	Elevated serum creatinine
Worsening renal function with ACEI or ARB	> 1.5 cm difference in kidney size on sonography
Recurrent flash pulmonary edema	
Examination	
Abdominal bruits	
Other bruits	
Advanced fundal changes	

Adapted from McLaughlin K, Jardine AG, Moss JG. Renal artery stenosis. Br Med J 2000;320:1124-1127.

The diagnosis seems unlikely in this patient for these reasons:

1) A prior captopril-enhanced isotopic renogram was normal.
2) Therapy with both an ACEI and an ARB have not normalized his BP (making unilateral renovascular disease less likely) while the serum creatinine has not risen markedly (making bilateral disease less likely).
3) The history is more suggestive of progressive idiopathic (essential) hypertension.
4) He does not have extensive atherosclerosis.

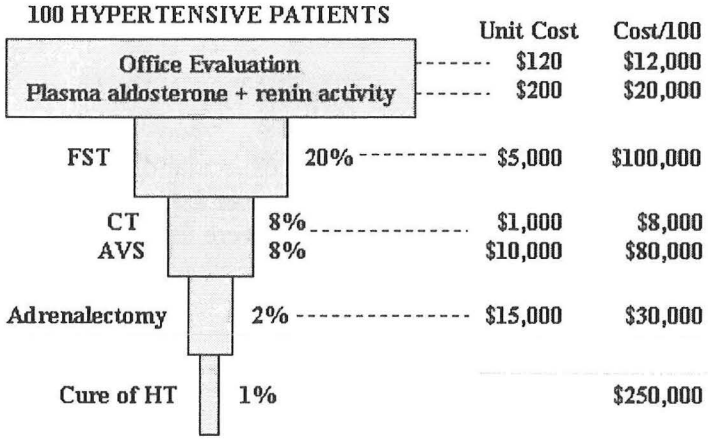
4. Primary Aldosteronism

Despite an ongoing literature blitz by Gordon (2001) and Stowasser (2001) from Brisbane that claims up to a 20% prevalence of primary aldosteronism among all hypertensives, only about 2% of selected patients with an elevated plasma aldosterone:renin ratio (ARR) turn out to have aldosterone-producing adenoma (APA) (Kaplan, 2002). This is less than the numbers of patients who harbor adrenal incidentalomas (Grossrubatscher et al., 2001). Such incidentalomas very rarely secrete excess aldosterone but may be a cause of subclinical Cushing's syndrome with insulin resistance (Terzolo et al., 2002).

The ARR does not have either good sensitivity or good specificity (Schwartz, 2002) and a high ARR usually reflects primarily a low plasma-renin (PRA) level (Montori et al., 2001). Since the majority of older hypertensives, particularly blacks, have a low PRA from reduced numbers of functioning juxta-glomerular cells, a normal plasma aldosterone (PA) with a typically low PRA will usually give a high ARR. Rather than using the basically flawed ARR, the PRA amd PA levels should simply be considered: if the PRA is low (below 0.5 ng/ml/hr) and the PA is high (above 20 μg/dL), the likelihood of primary aldosteronism is high enough to require additional screening tests (Figure 7). Either an intravenous saline (Holland et al., 1984) or oral salt (Young, 1997) loading test will give evidence for autonomous

hyperaldosteronism, although the Brisbane workers insist on a much more difficult and expensive Florinef Suppression Test (FST).

FIGURE 7
Cost of Workup for Primary Aldosteronism in 100 Patients to Achieve Cure of One



Only if high aldosterone levels cannot be normally suppressed should an adrenal CT scan and adrenal venous sampling (AVS) be obtained. The CT scan will often be misleading (Magill et al., 2002) so all experts now recommend AVS to confirm the site of aldosterone overproduction (Rossi et al., 2001). Unfortunately, the AVS, even in very experienced hands, may not be successful in up to 20% of patients with ambiguous CT findings and, successful or not, costs from $6,000-10,000.

For these and other reasons, I believe the workup for PA should be limited to hypertensives with unexplained hypokalemia, patients with a family history of aldosteronism, and some with truly resistant hypertension (Kaplan, 2001). For the latter group, a therapeutic trial with the aldosterone antagonist spironolactone or, in the near future, the more specific antagonist eplerenone which has fewer side effects (Funder et al., 2000) will be adequate. An aldosterone antagonist may prevent cardiac and renal fibrosis (Neumann et al., 2002) so may be a more logical potassium-sparer with a thiazide than triamterene (Ouzan et al., 2002).

This patient was not screened because he has a slightly low serum sodium (rather than a high level as seen in most PA patients, even if hypokalemia is not overt), a normal serum potassium and had not yet been found to be truly resistant to antihypertensive therapy. Nonetheless, if he does not respond adequately to an appropriate antihypertensive regimen, spironolactone should be tried.

5. Pheochromocytoma

There is no reason to suspect a pheo in this patient but, if there were, a single plasma metanephrine assay is now the best test to rule it in or out (Lenders et al., 2002).

B. Management of Other Cardiovascular Risk Factors

1. Assessment of Overall Risk

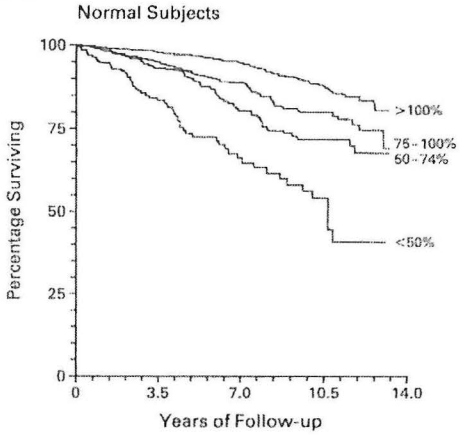
The Expert Panel report (2001) provides a simple way to determine individual patient's 10-year absolute risk for coronary disease (Appendix 2). Although it is obvious that patients such as Mr. HR are at high risk, providing an actual risk estimate may help motivate patients to reduce those risks that can be altered.

HB's absolute risk for coronary disease within 10 years is over 30%.

2. Dealing with Multiple Risks

The major risk factors are likely potentiated by others including physical inactivity (Snell and Mitchell, 1999) and reduced exercise capacity (Myers et al., 2002) (Figure 8).

FIGURE 8



Survival curves for normal subjects stratified according to the percentage of age-predicted exercised capacity achieved during an initial treatment test who were followed for 14 years (From Myers et al. 2002.)

HB has these risk factors:

- *Elevated systolic blood pressure*
- *Dyslipidemia*
- *Smoking*
- *Obesity, predominantly abdominal*
- *Physical inactivity*
- *Excessive alcohol intake*

Furthermore, he has target organ damages including LVH, proteinuria, and renal insufficiency.

C. Management of Resistant Hypertension

1. Search for Pseudo-resistance

Before starting the search for causes and solutions of resistance, out-of-office readings should be obtained to rule out the super-imposition of a significant "white-coat" effect. In one series of 118 patients with resistance (office BP > 140/90 while on 3 or more antihypertensive drugs), 28% had awake ambulatory BP less than 135/85 (Brown et al., 2001). These pseudo-resistant patients are at much lower risk for future CV events than are those with true resistance (Redon et al., 1998). They need not have more therapy to bring their office readings down to below 140/90 unless they have significant target organ damage. If TOD is present, more therapy is needed and no search for pseudo-resistance need be done.

2. Search for Non-adherence to Therapy

Patient non-adherence to prescribed therapy is often suspected but physician non-adherence to recommended guidelines is a more common cause of resistance. In a prospective study using an accurate monitor of drug adherence, 82% of those resistant to therapy were compliant, the same percentage as seen in those who were responsive. (Nuesch et al., 2001).

On the other hand, multiple studies have shown that physicians often do not increase the doses or numbers of drugs despite clear evidence of inadequate control (Berlowitz et al., 1998; Hyman and Pavlik, 2001; Oliveria et al., 2002). The willingness of practitioners to accept an elevated systolic BP as safe and not to require lowering plays a large role in this non-compliance.

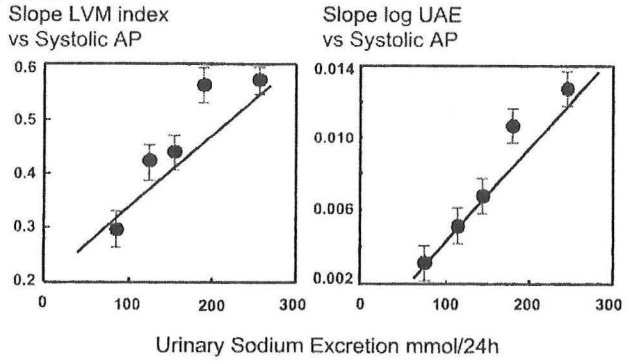
3. Lifestyle Modifications

In addition to drugs to reduce blood pressure and correct dyslipidemia, lifestyle modifications (Table 7) are critical for this and most hypertensives. A lower calorie diet, moderation of alcohol, and gradual increase of aerobic exercise should be the foundations. Smoking cessation, though the most effective way to immediately reduce risk, may be postponed until other changes are in place.

Recent publications reaffirm the value of lifestyle modifications in both preventing CV disease and lowering BP:

- Smoking cessation slows progression of nephropathy (Chuahirun and Wesson, 2002). Five strategies have been shown to significantly increase smoking quit-rates (Anderson et al., 2002).
    - Ask: systematically identify all tobacco users at every visit.
    - Advise: strongly urge all tobacco users to quit
    - Assess: determine willingness to make a quit attempt
    - Assist: aid the patient in quitting with a plan, counseling, medications, and educational materials
    - Arrange: schedule follow-up contact
- Weight loss improves endothelial function (Ziccardi et al., 2002).
- Aerobic exercise reduced BP by an average 4.9/3.7 mm Hg in 15 RCTs (Whelton et al., 2000).
- Dietary sodium reduction lowers BP beyond the effect of a diet rich in fruits and vegetables and low in fat (the DASH diet) (Sacks et al., 2001). At the same time, an amplification of CV damage manifested by LVH and proteinuria by high sodium intake has been demonstrated (du Caillar et al., 2002) (Figure 9).

FIGURE 9



Relationship between the values of slope (±SEM) of the relationship between systolic arterial pressure (AP) and left ventricular mass (LVM) index ($g/m^{2.7}$) in males (left) and urinary albumin excretion (UAE) in all patients (right) and mean values of urinary sodium excretion in each quartile. (From du Caillar et al., 2002.)

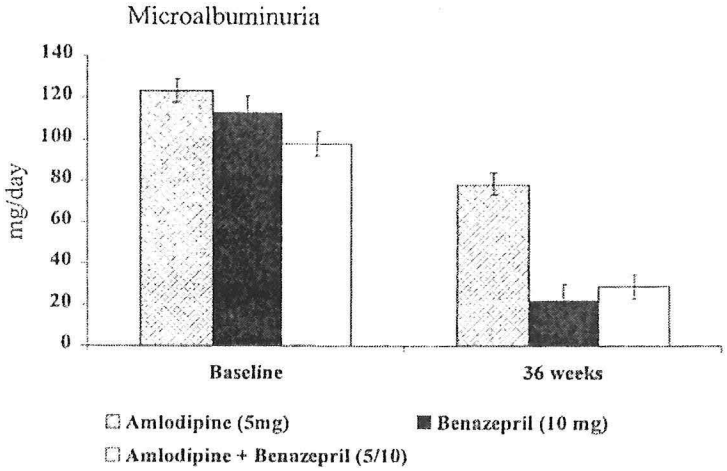
- Reduction of excessive alcohol intake lowers BP (Xin et al., 2001) whereas, as noted previously, those who consume moderate alcohol have less arterial rigidity (Hongaku et al., 2001) and a reduced risk of dementia (Ruitenberg et al., 2002) compared to those who abstain.

4. Antihypertensive Drugs

The overall algorithm for treatment (Figure 6) needs modification if BP control is not achieved with moderate doses of three or more drugs always including a diuretic. These include:

- *Increase in dose of diuretic* to ensure maintenance of slight contraction of intravascular volume. For those with intact renal function (serum creatinine $\leq$ 1.5 mg/dl), more HCT, up to 50 mg q a.m., should be adequate. For those with impaired renal function (serum creatinine >1.5 mg/dl), a more potent diuretic is needed, preferably once-a-day metolazone (2.5 up to 10 mg q a.m.) or 2-3 doses of furosemide, one dose in early a.m., another prior to dinner.
- *An ACEI or an ARB should be given*, almost always with a diuretic, to high-risk patients as shown in the HOPE, PROGRESS, and LIFE trials (Heart Outcomes, 2000; PROGRESS, 2001; Dahlöf et al., 2002).
- *A CCB may be needed as the third choice* in those with renal insufficiency and proteinuria, after an ACEI or ARB and a diuretic. When used as first choice, as in the AASK trial (Agodoa et al., 2001), a CCB will not be as renoprotective as an ACEI or ARB. When given with an ACEI, the CCB will lower BP further and will not prevent the renoprotective effect of the ACEI (Bakris et al., 2002) (Figure 10).

FIGURE 10



Changes from baseline in mean values of microalbuminuria at 36 weeks by type of therapy in 27 hypertensive patients with type 2 diabetes randomly assigned to one of three regimens. (Data from Bakris et al., 2002.)

- *Maximal doses of second and third choices*, e.g. 80 mg of most ACEIs, 20 mg of CCBs such as amlodipine or felodipine. Combinations of ACEIs and ARBs are being widely used but there is currently no evidence that they are more than simply additive or that adding one to maximal doses of the other provides additional effect (Agarwal, 2001).
- *For a fourth agent, labetalol* provides both beta- and alpha-blockade and is usually well tolerated. It must be given twice a day.
- *For a fifth agent, a central alpha-agonist* may be effective. There is no rational reason to use oral clonidine for a number of reasons, including:
    - To provide 24-hour coverage, it must be given three times a day, every eight hours; it should never be given only at bedtime since a rebound will likely occur every morning.
    - The dryness of the mouth and sedative effects are often bothersome.
    - A clonidine patch may be satisfactory if it does not cause skin irritation but my preference is to avoid clonidine. If a central alpha-agonist is considered to be essential (or affordable compared to other choices), guanfacine (Tenex, 1-3 mg/d) is a once-a-day agent with much less propensity to rebound and much better patient adherence.
- *For men with renal insufficiency, minoxidil* remains an effective vasodilator, but its use mandates adequate sympathetic blockade and large doses of potent diuretic.

Other maneuvers may be helpful, including:

- *Avoidance of all NSAIDs*, both first and second generations. The COX-2 specific inhibitors are just as likely to inhibit renal prostaglandins (Khan et al., 2002) and interfere with the efficacy of most antihypertensive drugs with the exception of CCBs (Frishman, 2002).
- *Avoidance of other agents* which may be inactivating or otherwise interfering with antihypertensive drug efficacy, e.g. rifampin (Flockhart and Tanus-Santos, 2002). Fortunately, most interactions increase efficacy, e.g. grapefruit juice with felodipine.
- *Reduction in LDL-cholesterol* (Ferrier et al., 2002) *and increase in HDL cholesterol* (Spieker et al., 2002) improve endothelial function and may lower BP.
- *Relief of chronic pain and anxiety* may lower BP (Linden et al., 2001).
- *Use of once-a-day formulations* instead of multiple doses.
- *Involvement of patient* by home BP monitoring and frequent contact with nurses and other personnel.

D. The Goal of Antihypertensive Therapy

As noted earlier, the mistaken acceptance of a high systolic BP as safe and appropriate is a major reason why practitioners often do not provide adequate therapy. The appropriate goals should be recognized and enough therapy should be provided to reach those goals in a timely manner.

The goals of therapy are different for low risk and high risk patients (Table 11 and 12). These tables are from the soon-to-be-published 2002 revision of the 1999 WHO-ISH guidelines (Guidelines Subcommittee, 1999) and is similar to the stratification of risk in the 1997 JNC-6 report (Joint National Committee, 1997).

Table 11. Factors Influencing Prognosis

Risk factors for cardiovascular disease used for risk stratification	Target-organ damage	Associated clinical conditions
• Levels of systolic and diastolic blood pressure (grades 1-3) • Men >55 years • Women >65 years • Smoking • Total cholesterol >5.1 mmol/l (200 mg/dl) • Raised LDL cholesterol >2.5 mmol/l (100 mg/dl) • Reduced HDL cholesterol M <1.0, F <1.2 mmol/l (<40, <45 mg/dl) • Family history of premature cardiovascular disease	• Left ventricular hypertrophy (electrocardiogram or echocardiogram) • Microalbuminuria (30-300 mg/day) • Ultrasound or radiological evidence of atherosclerotic plaque (carotid, iliac and femoral arteries, aorta) • Generalized or focal narrowing of the retinal arteries	Cerebrovascular disease • Ischemic stroke • Cerebral hemorrhage • Transient ischemic attack Heart disease • Myocardial infarction • Angina • Coronary revascularization • Congestive heart failure Renal disease • Diabetic nephropathy • Renal impairment (plasma creatinine concentration: F >1.4, M >1.5 mg/dl • Albuminuria >300 mg/day Peripheral vascular disease Diabetes

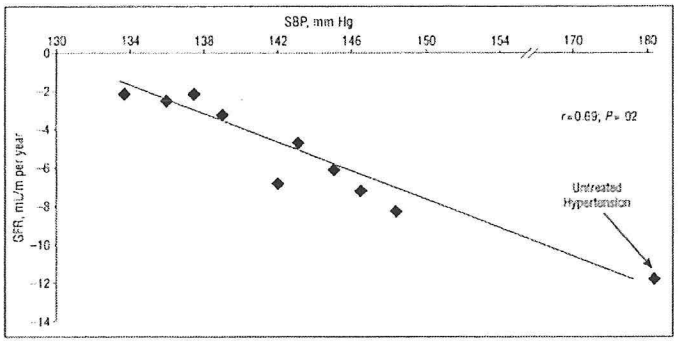
Table 12. Stratification of Risk to Quantify Prognosis

Other risk factors and disease history		Blood Pressure (mm Hg)		
		Grade 1 Mild hypertension SBP 140-159 or DBP 90 99	**Grade 2 Moderate hypertension SBP 160-179 or DBP 100-109**	**Grade 3 Severe hypertension SBP ≥180 or DBP ≥110**
I	No other risk factors	Low risk	Medium risk	High risk
II	1-2 risk factors	Medium risk	Medium risk	Very high risk
III	3 or more risk factors, target organ disease, or associated clinical conditions	High risk	High risk	Very high risk

- For low and medium risk patients, the goal should be <140/<90.
- For high or very high risk patients, including all diabetics, the goal should be <130/<80. In those with CRD, an even lower goal may be appropriate (Bakris et al., 2001). More intensive BP control, down to an average of 128/75, has been shown to protect normotensive type 2 diabetics from progression of nephropathy, retinopathy, and stroke compared to less intensive therapy, averaging 137/81 (Schrier et al., 2002).
- For elderly with isolated systolic hypertension, the systolic goal should be <140.

Reaching the goal may require multiple drugs. This need has been most clearly defined in hypertensives with proteinuric renal insufficiency, both diabetic and non-diabetic (Bakris et al., 2001) (Figure 11).

FIGURE 11

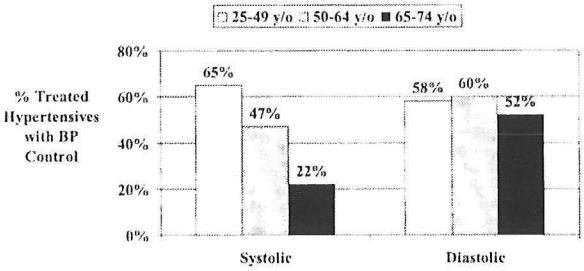


Rates of decline in glomerular filtration rate (GFR) vs the systolic blood pressure (SBP) in studies extending for three years or more in patients with type 2 diabetes mellitus nephropathy. (Data from Bakris et al., 2001.)

The goal is much less frequently reached for the systolic BP than for the diastolic BP, particularly in the older population (Banegas et al., 2002; Mancia et al., 2002) (Figure 12).

FIGURE 12

Percent of Treated Hypertensives with Systolic or Diastolic BP Control



Data from Mancia et al. *Arch Intern Med* 2002;162:582.

The percentage of 398 hypertensives on treatment grouped into three age categories whose office BPs were below 140/90 and home BPs were below 132/83. (Data from Mancia et al., 2002.)

At the same time, systolic elevations have been clearly shown to be associated with greater risk for cardiovascular disease than diastolic elevations (Benetos et al., 2002b) (Table 13). Thus, though harder to accomplish, control of systolic BP is the primary goal for most patients.

Table 13. Cardiovascular Mortality Rates in 4,714 hypertensive Over 14 Years by Levels of Systolic or Diastolic BP in Men Treated for Hypertension

Systolic BP	Mortality Rate Per 10,000 Person-Years	Diastolic BP	Mortality Rate Per 10,000 Person-Years
<140	15.4	<90	31.7
140-159	37.4	90-99	42.1
≥160	66.6	≥100	53.9

(Data from Benetos et al. 2002b.)

The changes recommended for patient HB were:

Lifestyle modifications

1. *Begin daily aerobic exercise, gradually increasing level*
2. *Reduce alcohol intake to no more than 2 drinks/day*
3. *Stop smoking; provide nicotine patch and bupropion (Wellbutrin)*
4. *Lose weight by diet And exercise.*

Antihypertensive regimen

Immediate

1. *Substitute metolazone, starting at 2.5 mg q a.m. for furosemide.*
2. *Discontinue valsartan.*
3. *Increase quinapril to 80 mg q a.m.*
4. *Increase labetalol to 200 mg bid*
5. *Discontinue metoprolol*
6. *Discontinue clonidine gradually*

Subsequent if needed

7. *Add amlodipine, starting at 5 mg q a.m.*
8. *Add spironolactone, starting at 25 mg q a.m.*

Additional changes

9. *Substitute acetaminophen for NSAID*
10. *Add a statin*
11. *If erectile dysfunction persists, consider sildenafil*

IV. CONCLUSION

These two patients demonstrate some of the major problems clinicians face in the diagnosis, evaluation, and treatment of hypertension. Fortunately, these and other problems that interfere with appropriate management can usually be solved. And, more fortunately, most currently inadequately treated hypertensives need only modest modifications of lifestyle and more antihypertensive drug therapy to achieve adequate control. The payoffs, both for the individual and for society at large, are well worth the effort.

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APPENDIX 1

HYPERVENTILATION: PATIENT INFORMATION

Hyperventilation or overbreathing is a common mechanism for a variety of symptoms, including a sensation of breathlessness; dizziness and lightheadedness; headache; chronic fatigue; rapid heart rate, sometimes associated with discomfort or pain in the chest; tingling, numbness or a feeling of "falling asleep" in the fingers; spots before the eyes, and ringing in the ears. Occasionally, it causes fainting with a loss of consciousness.

Most hyperventilation is caused by a subconscious (involuntary) reaction to stress or anxiety that the patient may not be aware of experiencing.

The symptoms are caused by a lack of oxygen in various parts of the body; in the brain, this results in dizziness; in the heart, a faster and harder heart rate; in the fingers, tingling or numbness. The problem arises from a chemical change in the blood. With overbreathing, more of the gas carbon dioxide is exhaled. The carbon dioxide is an acid, so that the body becomes more alkaline. The alkalinity of the blood prevents the release of oxygen from the red blood corpuscles which carry oxygen from the lungs to various parts of the body. Since, oxygen does not break away from the blood cells, the body has a deficiency of oxygen, interfering with the normal function of the various organs.

If the problem cannot be prevented by slowing down the rate of breathing, the symptoms can be quickly reversed by rebreathing into a paper sack held tightly over the mouth and nose. Thereby carbon dioxide is replenished, the alkaline condition is reversed, and the blood cells release oxygen in a normal way, so the oxygen deficiency is overcome. There is no danger from rebreathing from a paper sack, so this may be performed as often as needed, preferably when any symptoms are first noted.

APPENDIX 2

Estimate of 10-Year Absolute Risk for Coronary Heart Disease

Based on Framingham Point Scores

A: Estimate of 10-Year Risk for Men

Age, y	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Total Cholesterol, mg/dL	Points				
	Age 20-39y	Age 40-49 y	Age 50-59 y	Age 60-69 y	Age 70-79 y
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
≥280	11	8	5	3	1

	Points				
	Age 20-39y	Age 40-49 y	Age 50-59 y	Age 60-69 y	Age 70-79 y
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL, mg/dL	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP, mm Hg	If Untreated	If Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

Point Total	10-Yer Risk, %
<0	<1
0	1
1	1
2	1
3	1
4	1
5	2
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
≥17	≥30

B: Estimate of 10-Year Risk for Women

Age, y	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

Total Cholesterol, mg/dL	Points				
	Age 20-39 y	Age 40-49 y	Age 50-59 y	Age 60-69 y	Age 70-79 y
<160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1
240-279	11	8	5	3	2
≥280	13	10	7	4	2

	Points				
	Age 20-39 y	Age 40-49 y	Age 50-59 y	Age 60-69 y	Age 70-79 y
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL, mg/dL	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP, mm Hg	If Untreated	If Treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
≥160	4	6

Point Total	10-Yer Risk, %
<9	<1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
≥25	≥30

Adapted from Expert Panel. JAMA 2001;205:2497.