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MEDCO

CONTAINMENT SERVICES, Inc.

MANAGING CARE FOR PRESCRIPTION DRUG BENEFITS

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Medco's Background

* Nation's largest drug benefit administrator

* Medco covers Benefit Plans with 34 million beneficiaries

* 33 million prescriptions filled annually through mail service

* 50 million prescriptions filled annually through retail PPOs

* $2.5 billion in mail service drug spend/$5 billion retail

* Intervention strategies to control drug spend

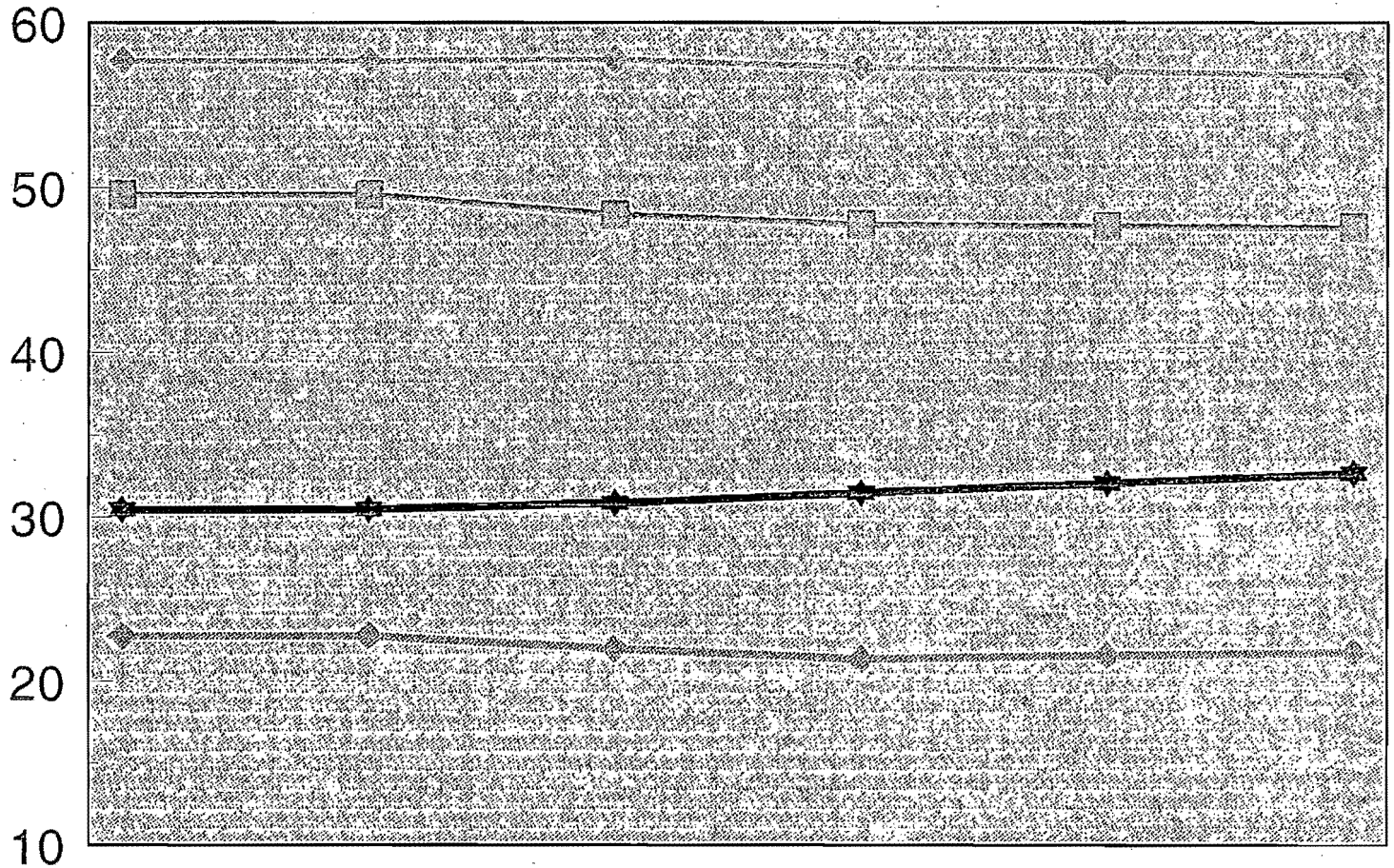
  - Prescriber's Choice
  - Formularies (Closed and Incentive-based)
  - Mail Service for maintenance medications
  - Discounted retail pharmacy PPOs
  - Physician and Patient Education
  - Drug Utilization Review

Sample Conversion Rates by Therapeutic Category

Category	Conversion Rate
H_2 Antagonist	36%
Non-Sedating Antihistamine	34%
Cholesterol Reducing Agents	55%
Calcium Channel Blockers	16%
ACE Inhibitors	46%

Prescriber's Choice Market Share Changes

Medco Containment Services, Inc.



	MAR 92	MAR 92	JUN 92	SEP 92	DEC 92	MAR 93
PREFERRED DRUG						
(Non-PC Clients)	22.7	22.7	21.9	21.3	21.5	21.7
(PC Clients)	30.4	30.4	30.8	31.4	32.0	32.6
NON-PREFERRED DRUG						
(Non-PC Clients)	57.6	57.6	57.7	57.2	57.0	56.7
(PC Clients)	49.5	49.5	48.3	47.7	47.6	47.5

Strategies for Managing Hypertension

OPTIMAL

THERAPEUTICS PROGRAM℠

Antihypertensive Regimens: Burgeoning Choices

■ As recently as the late 1970s, only a few drugs were available for the treatment of hypertension. The 1980s witnessed an explosion of new agents. While this offers the physician a wealth of choices, it also presents an increasingly difficult challenge in balancing efficacy, side effects, and costs in devising a regimen that will be lifelong for most patients.

DIURETICS

Amiloride, HCTZ (Moduretic)
Bendroflumethiazide (Naturetin)
Benzthiazide (Exna)
Benzthiazide (Praaqua)
Bumetanide (Bumex)
Chlorothiazide (Diuril)
Chlorthalidone (Hygroton)
Chlorthalidone (Thalitone)
Cyclothiazide (Anhydron)
Furosemide (Lasix)
HCTZ (Esidrix)
HCTZ (HydroDIURIL)
HCTZ (Oretic)
HCTZ, Triamterene (Dyazide)
Hydroflumethiazide (Diucardin)
Hydroflumethiazide (Saluron)
Hydroflumethiazide, Reserpine (Salutensin/Salutensin-Demi)
Indapamide (Lazol)
Methyclothiazide (Aquatensen)
Methyclothiazide (Enduron)
Methyclothiazide, Deserpidine (Enduranyl)
Methyclothiazide, Reserpine (Diutensen-R)
Metolazone (Diula)
Metolazone (Mykrox)
Metolazone (Zaroxolyn)
Polythiazide (Renese)
Polythiazide, Reserpine (Renese-R)
Spironolactone (Aldactone)
Spironolactone, HCTZ (Aldactazide)
Triamterene +HCTZ, (Diazide)
Triamterene, HCTZ (Maxzide)
Trichlormethiazide (Metahydrin)

BETA BLOCKERS

Acebutolol (Sectral)
Atenolol (Tenormin)
Atenolol, Chlorthalidone (Tenoretic)
Betaxolol (Kerlone)
Carteolol (Cartrol)
Labetalol (Normodyne)
Labetalol (Trandate)
Labetalol, HCTZ (Normozide)
Labetalol, HCTZ (Trandate HCT)
Metoprolol (Lopressor)
Metoprolol, HCTZ (Lopressor HCT)
Nadolol (Corgard)
Nodolol, Bendroflumethiazide (Corzide)
Penbutolol (Levotol)
Pindolol (Visken)
Propranolol (Inderal)
Propranolol (Inderol LA)
Propranolol, HCTZ (Inderide)
Propronolol, HCTZ (Inderide LA)
Timolol (Blocadren)
Timolol, HCTZ (Timolide)

CALCIUM CHANNEL BLOCKERS

Diltiazem (Cardizem)
Diltiazem (Cardizem SR)
Felodipine (Plendil)
Isradipine (DynoCirc)
Nicardipine (Cardene)
Nifedipine (Adalat)
Nifedipine (Procardia)
Nifedipine (Procardia XL)
Verapamil (Calan)
Verapamil (Calan SR)
Verapamil (Isoptin)
Verapamil (Isoptin SR)
Verapamil (Verelan)

ACE INHIBITORS

Benazepril (Lotensin)
Captopril (Capoten)
Captapril, HCTZ (Capozide)
Enalapril (Vasotec)
Enalapril, HCTZ (Vaseretic)
Fosinopril (Monopril)
Lisinopril (Prinivil)
Lisinopril (Zestril)
Lisinapril, HCTZ (Prinzide)
Lisinapril, HCTZ (Zestoretic)
Ramipril (Altace)

OTHER

Clonidine (Catapres)
Clonidine (Catapres-TTS)
Clonidine, Chlorthalidone (Combipres)
Deserpidine (Harmonyl)
Doxazosin (Cardura)
Guanabenz (Wytensin)
Guanadrel Sulfate (Hylarel)
Guanethidine, HCTZ (Esimil)
Guanethidine (Ismelin)
Gaunfacine (Tenex)
HCTZ, Deserpidine (Oreticyl)
Hydralazine (Apresoline)
Hydrolazine, HCTZ (Apresazide)
Hydralazine, HCTZ (Apresoline-Esidrix)
Hydralazine, HCTZ, Reserpine (Ser-Ap-Es)
Mecamylamine (Inversine)
Methyldopa (Aldomet)
Methyldopo, Chlorothiozide (Aldoclor)
Methyldopa, HCTZ (Aldoril)
Minoxidil (Loniten)
Prazosin (Minipress)
Prozosin, Polythiozide (Minizide)
Quinethazone (Hydromox)
Quinethazone, Reserpine (Hydromox R)
Rauwolfio Serpentina (Raudixin)
Rauwolfia Serpentina, Bendroflumethiazide (Rauzide)
Reserpine (Serpasil)
Reserpine, Chlorothiazide (Diupres)
Reserpine, HCTZ (Hydropres)
Reserpine, HCTZ (Serpasil-Esidrix)
Reserpine, Hydralazine (Serpasil-Apresoline)
Terazosin (Hytrin)

When High Blood Pressure Isn't Hypertension

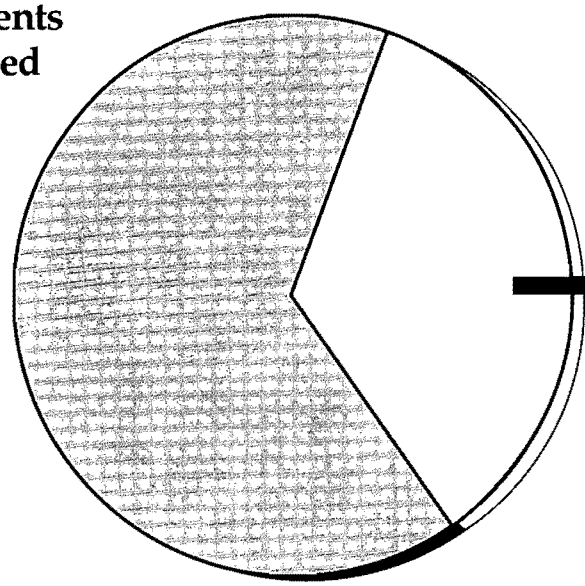
■ True hypertension is common, occurring in about a fifth of American adults.[1] In the 1970s, undetected hypertension was a major public health problem and it remains an important issue in populations with limited access to medical care, such as minorities and the poor.

However, for those who have ongoing contact with the health care system, blood pressure screening has become so common that occasionally the reverse problem occurs: labeling patients as "hypertensive" when they don't actually have this condition.

■ Like many biological systems, blood pressure is variable throughout the day, and can be artificially raised by a number of external factors, particularly transient anxiety – so-called "white-coat" hypertension.[2]

Cigarette smoking, caffeine, and alcohol can also raise blood pressure acutely.[3,4] Because of this variability, except in extreme cases, a patient should not be diagnosed as hypertensive and committed to a therapeutic regimen based on only one or two readings.

Framingham Study:[5] Follow-up on patients originally diagnosed as hypertensive but not put on therapy



31%
normotensive on subsequent visits

Recommendations:

■ Repeat blood pressure measurements two or three times at each visit when a diagnosis of hypertension is being considered.

■ Unless extremely high values are found, document hypertension (systolic >140 mmHg, diastolic > 90 mmHg) on three separate visits before making the diagnosis.

■ Do not base a diagnosis of hypertension on blood pressure readings made when a patient is in acute pain or a state of anxiety.

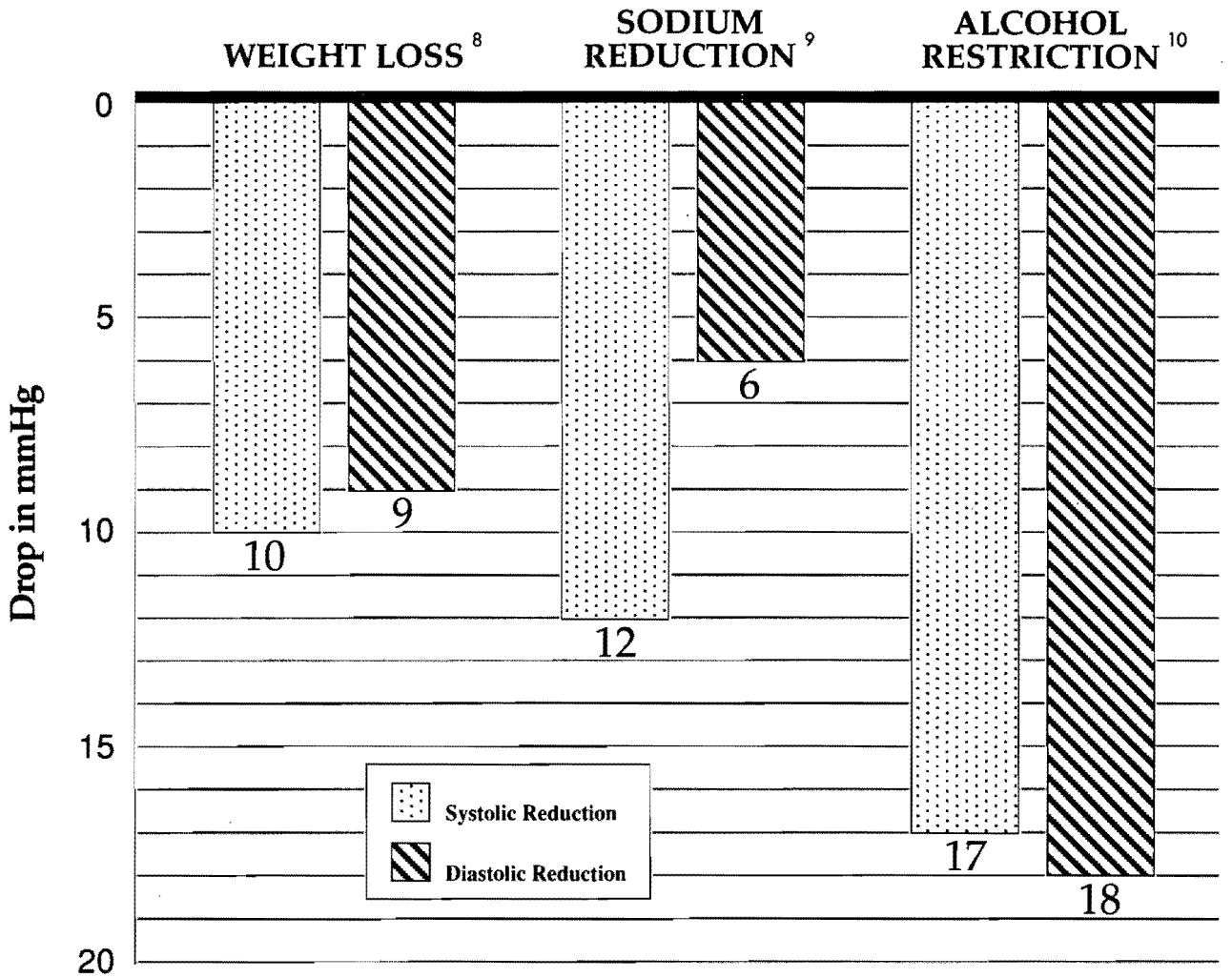
■ Consider whether some or all of the elevation in blood pressure may be the result of acute exogenous factors such as caffeine intake, nicotine, alcohol use, drugs or "white-coat," rather than "true" essential hypertension.

How Well Do Non-Drug Measures Really Work?

■ Over the years, a variety of non-drug treatments have been proposed for hypertension, ranging from unusual diets to transcendental meditation.[6]

While conventional wisdom holds that such measures are not very effective, well-controlled studies have shown that weight loss, reduction of dietary salt, and elimination of excess alcohol use can have substantial impact in lowering blood pressure.[7]

Reduction in Systolic and Diastolic Blood Pressure with Specific Non-Drug Approaches



Recommendations:

■ Weight loss: to within 15% of ideal body weight

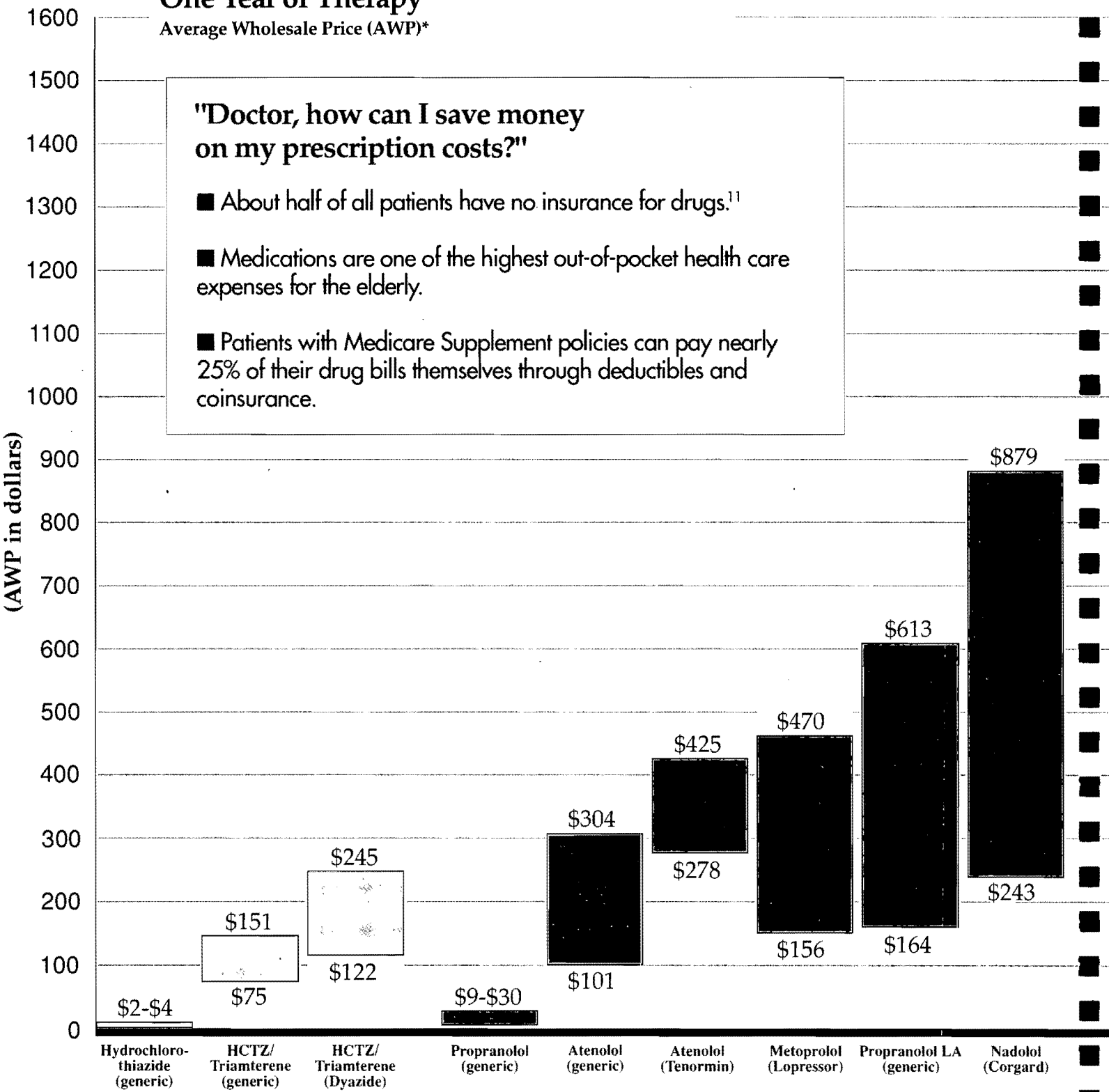
■ Salt reduction: 4-6g salt per day ($1\frac{1}{2} - 2\frac{1}{2}$g sodium)

■ Alcohol restriction: reduce to 1 oz. ethanol per day (2 oz. whiskey, 8 oz. wine, or 24 oz. beer)

The Price of Normotension

One Year of Therapy

Average Wholesale Price (AWP)*



THIAZIDES

Doses used to determine cost:[12]

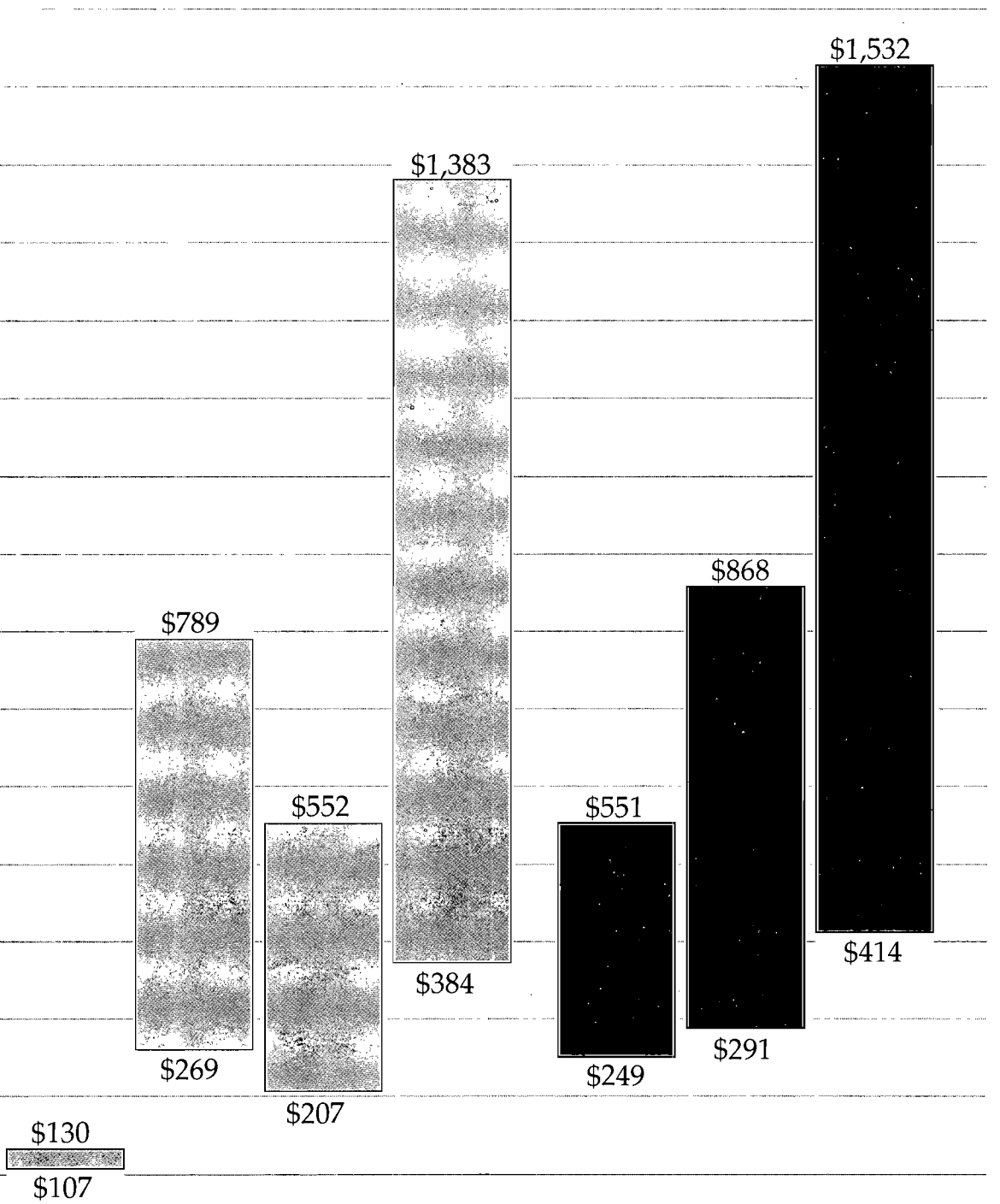
HCTZ (generic)	12.5 - 50 mg
HCTZ/Triamterene (generic)	one - two 25 mg/50 mg
HCTZ/Triamterene (Dyazide)	one - two 25 mg/50 mg

BETA BLOCKERS

Propranolol	40 - 320 mg
Atenolol	25 - 100 mg
Metoprolol (Lopressor)	50 - 200 mg
Nodolol (Corgard)	20 - 240 mg

* Data on file, PAID Prescriptions, Inc. November 1991

NOTE: Prescription costs do not increase directly proportional to dose, i.e. the cost of a 40 mg dose is not twice the cost of a 20 mg dose.



Verapamil (generic)	Verapamil LA (generic)	Diltiazem (Cardizem SR)	Nifedipine (Procardia XL)	Lisinopril (Prinivil/Zestril)	Enalapril (Vasotec)	Captopril (Capoten)

CALCIUM ANTAGONISTS

Verapamil	120 - 480 mg
Diltiazem SR (Cardizem SR)	60 - 180 mg
Nifedipine (Procardia XL)	30 - 120 mg

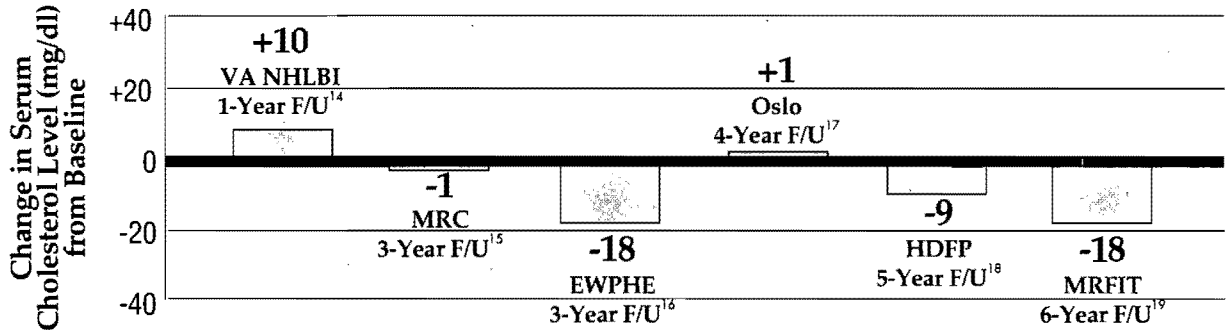
ACE INHIBITORS

Lisinopril (Prinivil/Zestril)	5 - 40 mg
Enalapril (Vasotec)	5 - 40 mg
Captopril (Capoten)	50 - 300 mg

Side Effects: Hazards Versus Hype

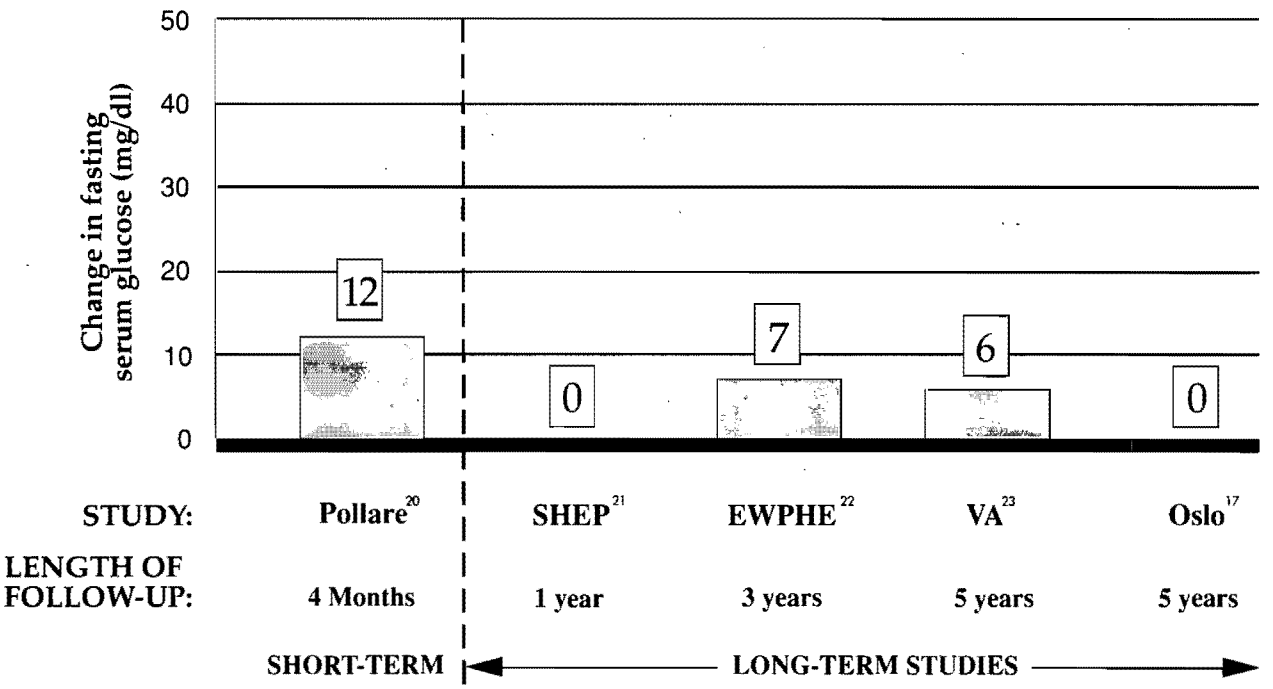
■ Recently, studies and newspaper articles have begun to appear highlighting the drawbacks of traditional hypertension therapy, particularly the thiazides. Following this publicity, across the country previously compliant patients have become alarmed and thiazide use has dropped precipitously.

Lipid Effects of Long-Term Thiazide Use



■ **The rise in lipids and glucose seen with thiazide therapy, if it occurs, is transient, with values returning to normal after a few months of therapy.[13]**

Thiazides and Glucose: Minimal Effect from Long-Term Use



■ **Tens of thousands of patients have been longitudinally studied in multi-center trials of thiazide treatment for hypertension, with careful metabolic monitoring. Changes in serum glucose have been found to be absent or clinically negligible, with no increase in risk of diabetes.**

■ In an unprecedented response to the heavy promotion of one such study, an eminent group of senior hypertension researchers (Moser, Blaufox, Freis, Gifford, Kirkendall, Langford, Shapiro, Sheps) wrote an editorial in the Journal of the American Medical Association. It said, in part:

"... none of the newer agents appear to combine all the favorable characteristics of thiazide diuretics (including their relatively low cost). Our clinical experience suggests that blood pressure control is often difficult to achieve without the use of a diuretic ... none of these [newer] agents, including angiotensin converting enzyme inhibitors, have been subjected to the rigorous clinical trials that are required to prove this assumption [that they will have a more favorable impact on coronary heart disease]."[24]

Doing Better but Feeling Worse?

■ In the 1980s, reports began to appear suggesting that important differences existed among anti-hypertensive drugs in terms of their effect on "quality-of-life" measures such as mood, sexual function, and perceived health. To address methodological problems with some of these early studies, a large multi-center randomized placebo controlled trial was conducted – the Trial of Antihypertensive Interventions and Management (TAIM).[25] The investigators closely followed some 700 hypertensive patients randomized to placebo, chlorthalidone, or atenolol.

■ Patients in all groups completed "quality of life" assessments including measures of distress as well as well-being.

ANTIHYPERTENSIVES AND "QUALITY OF LIFE"*

	PLACEBO (N=232)	CHLORTHALIDONE (N=227)	ATENOLOL (N=238)
Total Physical Problems	0.15 ↑	0.16 ↑	0.14 ↑
Overall Psychological Functioning	0.04 ↑	0.15 ↑	0.14 ↑
Overall Life Satisfaction	0.04 ↓	0.04 ↑	0.02 ↑
Sexual Physical Problems	0.12 ↑	0.06 ↑	0.09 ↑
Depression	0.15 ↑	0.15 ↑	0.14 ↑
Anxiety	0.14 ↑	0.17 ↑	0.15 ↑
Sleep Disturbances	0.29 ↑	0.23 ↑	0.26 ↑
Fatigue	0.20 ↑	0.17 ↑	0.15 ↑
Satisfaction with Physical Health	0.21 ↑	0.27 ↑	0.19 ↑
Sexual Satisfaction	0.14 ↓	0.02 ↓	0.04 ↑

From Wassertheil - Smoller, S. Ann Int Med 1991; 114:613-20

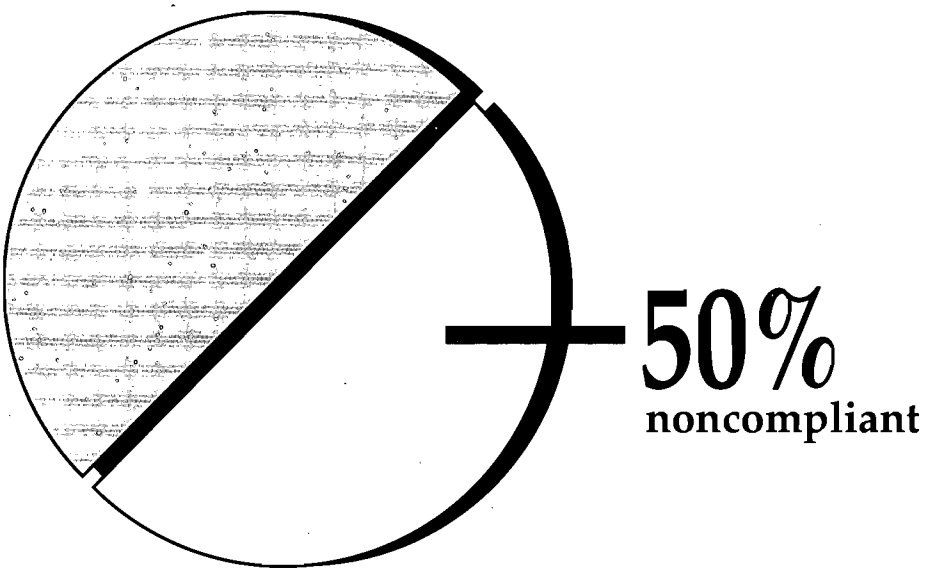
* Data are presented as mean change between baseline and six months. Responses were on a scale ranging from 0 (not at all) to 4 (extremely).

■ Overall, "quality of life" measures actually improved slightly in all treatment groups, and there were no significant differences between drug groups and placebo-treated controls. Interestingly, the only treatment associated with significant improvement in perceived quality of life was weight reduction, regardless of drug therapy used. The subgroup of men randomized to the no dietary modification/chlorthalidone group did report a higher frequency of erection problems, highlighting the need for careful history-taking concerning side effects in such patients.

Noncompliance: A Major Epidemic

■ No matter how well conceived the regimen, a drug not taken by the patient cannot achieve its intended effect. Studies of actual patient behavior have produced disarming and disheartening results: the frequency with which patients do not adhere to prescribing regimens is surprisingly high. Often, cost is cited as a reason for noncompliance or for "stretching out the prescription."

Compliance of patients on long-term therapy after one year [26,27]



Recommendations:

■ Check refill dates on current medications; call the patient's pharmacist if questions arise.

■ Use non-threatening questions to detect poor compliance, such as "Most people have trouble taking all of their pills. Do you have any trouble taking all of yours?"

■ Make a compliance history an integral part of each visit.

■ Do not assume that lack of blood pressure control is the result of drug failure alone.

■ Discuss the need for therapy and possible side effects when initiating the prescription.

■ Design a regimen that is acceptable to the patient in terms of dosing frequency, side effects and cost.

■ Provide simple oral and written instructions.

■ "Un-clutter" the overall drug regimen by eliminating drugs that are not necessary: the more drugs, the lower the compliance.

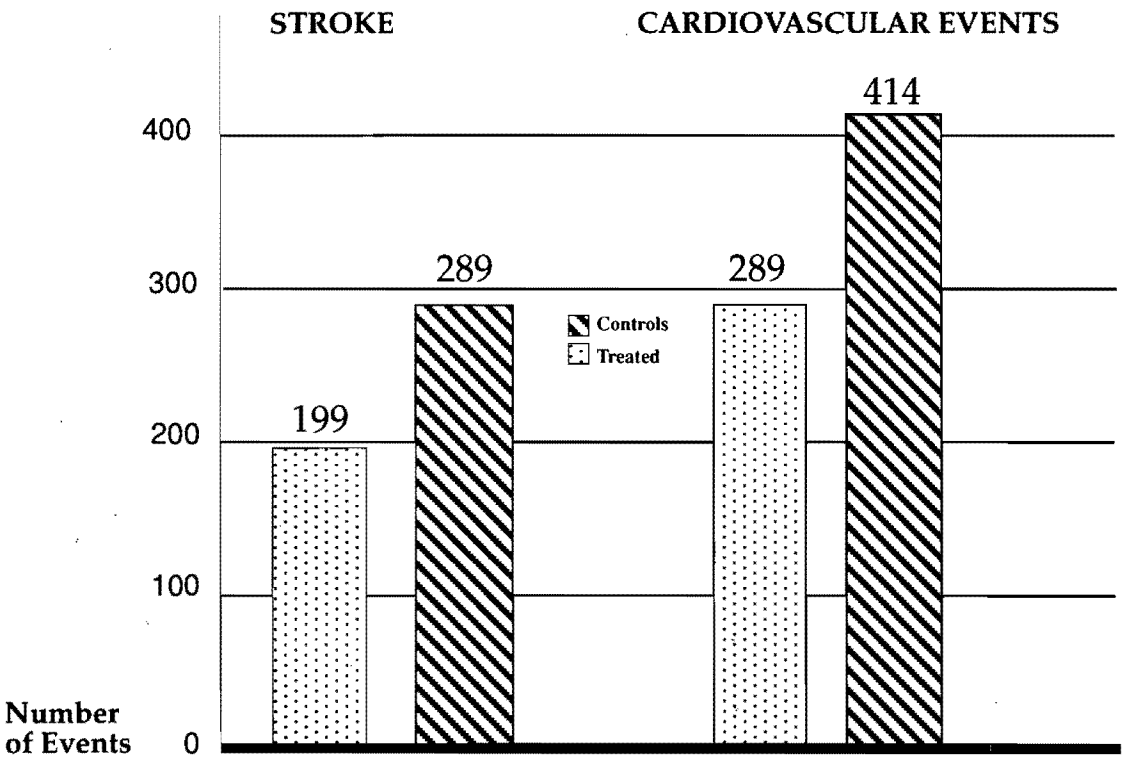
■ Enlist family members or care-givers in ensuring proper drug use.

Treating Isolated Systolic Hypertension in the Elderly: New Studies Demonstrate Benefit Exceeds Risk

■ For years, there has been uncertainty over whether to treat isolated systolic hypertension (ISH) in older patients. Data have recently emerged to justify treatment of ISH (systolic blood pressure >160 in the face of diastolic pressure < 90).

■ In a 1991 paper, the Systolic Hypertension in the Elderly Project (SHEP) demonstrated that using a thiazide or beta blocker in elderly patients with ISH was effective in reducing morbidity and mortality even in old age.

Benefits of Treating Isolated Systolic Hypertension in the Elderly[28]



Recommendations:

■ Screen for hypertension, including ISH, in all patients regardless of age.

■ Unless specific clinical circumstances dictate otherwise, treat systolic BP >160 even with normal diastolic pressures.

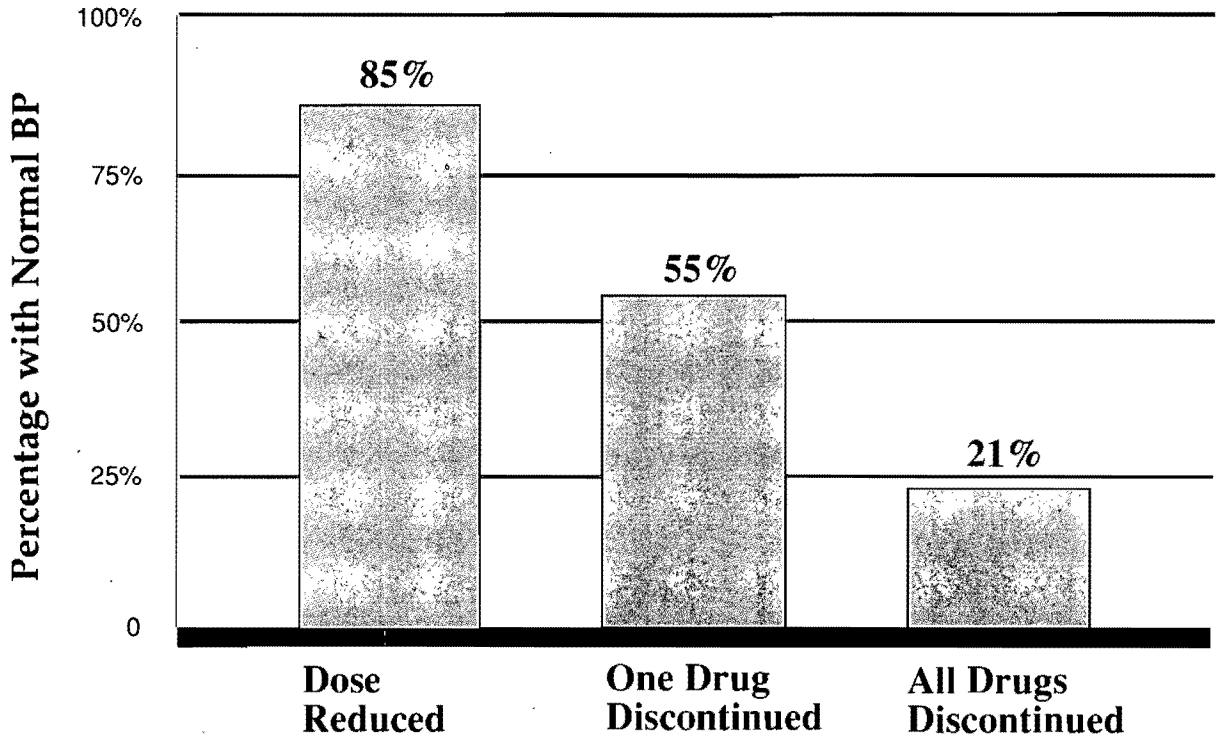
■ Thiazide and beta blocker therapy are the drugs shown to confer benefit in ISH.

Reassessing Drug Therapy

■ Because of non-pharmacologic treatments including weight loss, salt restriction, reduction of alcohol intake, or exercise, or perhaps because of initial misdiagnosis, some patients on chronic antihypertensive therapy will remain normotensive when therapy is reduced or withdrawn altogether.

■ Reducing therapy must be done cautiously, but such periodic reassessment of therapy is an important component of management. "Pruning" a therapeutic regimen to its essentials will reduce the frequency of adverse effects, lower cost, and increase compliance with those drugs that are truly needed.

Many Patients Remain Normotensive Following Reduction in Therapy[29,30]



Reduction in therapy may be appropriate for patients who are normotensive over a one year period.

Recommendations:

- Try non-pharmacologic management in patients with mild hypertension. Continue these measures if drug therapy becomes necessary.

- If non-pharmacologic measures are inadequate, initiate monotherapy with the most appropriate first-line drug for the individual patient. Considering all factors, this will be a diuretic or beta blocker in most cases.

- If blood pressure is still not adequately controlled, either take patient off the initial drug and replace with a first-line drug from another class or add a drug from another class. If a diuretic has not been chosen for initial therapy, it should be used.

- Treat older patients for isolated systolic hypertension (ISH), generally with a diuretic or a beta blocker.

- After one year of successful blood pressure control, reassess therapy to determine the lowest effective dose for each drug used. Maintaining compliance to the non-pharmacologic regimen is essential.

These recommendations represent a synthesis of the best available current clinical literature. However, specific patient care decisions will need to be tailored to the individual clinical circumstances of each patient.

References

1. Subcommittee on Definition and Prevalence of the 1984 Joint National Committee: Hypertension prevalence and the status of awareness, treatment, and control in the United States: Final report of the Subcommittee on Definition and Prevalence of the 1984 Joint National Committee. Hypertension 1985; 7:458-68.

2. Moncia G, Bertiner G, Grassi G, et al. Effects of blood pressure measurement by the doctor on patient's blood pressure and heart rate. Lancet 1983; 2:695-8.

3. Klotsky AL, Friedman GD, Siegelaub AB, et al. Alcohol consumption and blood pressure. Kaiser Permanente Multiphasic Health Examination Data. N Engl J Med 1987; 296:1194-1200.

4. Freestone S, Ramsey LE. Effect of coffee and cigarette smoking on the blood pressure of untreated and diuretic-treated hypertensive patients. Am J Med 1982; 73:348-53.

5. Konnel WB, Sorlie P, Gordon T. Labile hypertension: a faulty concept? The Framingham Study. Circulation 1980; 61:1183-7.

6. Kaplan NM. Non-drug treatment of hypertension. Ann Intern Med 1985; 102:359-73.

7. 1988 Joint National Committee. The 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1988; 148:1023-38.

8. Reisin E, Frohlich ED, Messerli FH, et al. Cardiovascular changes after weight reduction in obesity hypertension. Ann Intern Med 1983; 98: 315-19.

9. MacGregor GA, Markandu N, Best F, et al. Double-blind, randomized cross-over trial of moderate sodium restriction in essential hypertension. Lancet 1983; 1:1179-82.

10. Saunders JB, Beevers DG, Paton A. Alcohol-induced hypertension. Lancet 1981; 2:653-6.

11. Gallup G, Catugno HE. Preferences and practices of Americans and their physicians in antihypertensive therapy. Am J Med 1986; 81 (suppl 6C):20-4.

12. The Medical Letter on Drugs and Therapeutics, Drugs for Hypertension, Vol 33 (Issue 842) April 19, 1991

13. Moser M. Controversies in the management of hypertension. Amer Fam Pract 1990; 41:1449-60.

14. Veterans Administration – National Heart, Lung, and Blood Institute Cooperative Study on Antihypertensive Therapy. Mild hypertension: serum lipoprotein levels during chlorthalidone therapy. JAMA 1980; 244:1691-5.

15. Greenberg G, Brennan PJ, Miall WE. Effects of diuretic and beta-blocker therapy in the Medical Research Council Trial. Am J Med 1984; 76(2A):45-51.

16. Amery A, Birkenhager W, Bulpitt C, et al. Influence of antihypertensive therapy on serum cholesterol in elderly hypertensive patients: results of trial by the European Working Party on High Blood Pressure in the Elderly (EWPHE). Acta Cardiol 1982; 37:235-44.

17. Helgelond A. Treatment of mild hypertension: Five year controlled drug trial: The Oslo Study. Am J Med 1980; 69:725-32.

18. Hypertension Detection and Follow-up Program Cooperative Group. Five year findings of the Hypertension Detection and Follow-up Program: I. Reduction of mortality of persons with high blood pressure, including mild hypertension. JAMA 1979; 242:2562-71.

19. Caggiulo AW, Christakis G, Farrond M, et al. The Multiple Risk Factor Intervention Trial (MRFIT): IV. Intervention on blood lipids. Prev Med 1981; 10:443-75.

20. Pollore T, Lithell H, Berne C. A comparison of the effects of hydrochlorothiazide and captopril on glucose and lipid metabolism in patients with hypertension. N Engl J Med 1989; 321:868-73.

21. Hulley SB, Furberg CD, Gurland B, et al. Systolic Hypertension in the Elderly Program Study: anti-hypertensive efficacy of chlorthalidone. Am J Cardial 1985; 56:913-20.

22. Amery A, Birkenhager W, Brixto P, et al. Martality and marbidity results fram the Eurapean Working Party on High Blood Pressure in the Elderly Trial. Lancet 1985; 1:1349-54.

23. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Comparison of propranolol and hydrochlorothiazide for the initial treatment of hypertension:II. Results of long-term therapy. JAMA 1982; 248:2004-11.

24. Moser M, Blaufox MD, Freis E, et al. Who really determines your patients' prescriptions? JAMA 1991; 265:498-500.

25. Wassertheil-Smoller S, Blaufox MD, Oberman A, et al. Effect of antihypertensives on sexual function and quality of life: the TAIM study. Ann Intern Med 1991; 114:613-20.

26. Clark LT. Improving compliance and increasing contral af hypertension: needs of special reference populations. Am Heart J 1991; 121:664-9.

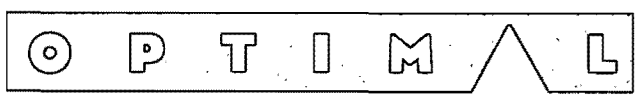
27. Sackett DL, Snaw JC. The magnitude of compliance and noncompliance. In Haynes RB, Taylor DW, Sackett DL (eds), Compliance in Health Care. Baltimore: Johns Hopkins, 1979, pages 11-22.

28. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. JAMA 1991; 265:3255-64.

29. Levinson PD, Khatri IM, Freis ED. Persistence of normal blood pressure after withdrawal of drug treatment for mild hypertension. Arch Intern Med 1982; 142:2265-8.

30. Finnerty FA. Step-down treatment of mild systemic hypertension. Am J Cardial 1984; 53:1304-7.

This information was prepared as part of the Optimal Therapeutics Program as an educational service to physicians. A more complete overview of antihypertensive drug use is provided in the accompanying monograph. For copies of the studies on which this material is based, or for other information, please contact the Optimol Therapeutics Progrom, One Gateway Center, Suite 402, Newton, Massochusetts 02158.



THERAPEUTICS PROGRAM[SM]

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