Hypertension in the Elderly

Can We Improve Results of Therapy?

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Awareness of and therapy for hypertension in the United States have been increasing in older patients. Despite this improvement, hypertension continues to be poorly controlled in this patient population. The control rate, defined as systolic blood pressure less than 140 mm Hg and diastolic blood pressure less than 90 mm Hg, is surprisingly low for older patients, despite abundant data documenting the reduction of cardiovascular events by treating both systolic-diastolic and isolated systolic hypertension. Comorbid diseases and physiological alterations in the elderly, including reduced myocardial contractility, renal function, total body water, baroreceptor responsiveness, and cognitive function, must be considered, but in general these have not limited the effectiveness of antihypertensive drug therapy.

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Recently, interest has been revived in the use of combination therapy for the treatment of hypertension. This approach has been supported by the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Complex drug regimens can result in noncompliance; adverse drug reactions are increased if high doses of a single drug are used, and excessive costs may be incurred if medication is dispensed separately. New fixed-dose combination antihypertensive drugs can simplify dosing regimens, improve compliance, improve blood pressure (BP) control, decrease dose-dependent adverse effects, and reduce cost. Combinations that include low doses of diuretics have proved effective without an increase in orthostatic hypotension. It is especially important that BP control be achieved in older patients to avoid the debilitating complications of stroke, heart failure, angina, and renal failure that may impair their quality of life. The use of combination therapy may help to increase the number of elderly patients whose hypertension is well controlled.

PREVALENCE

The prevalence of hypertension increases with aging. For women, the prevalence exceeds that of men between the fifth and sixth decade of life. According to the National Health and Nutrition Examination Survey III, 1988-1991, the prevalence of hypertension for those aged 65 to 74 years was 72% for African Americans, 53% for whites, and 55% for Mexican Americans. The actual distribution of elevated BP by level for the US population 60 years and older was 49.6% for stage 1 hypertension (140-159/90-99 mm Hg), 18.2% for stage 2 (160-179/100-109 mm Hg), and 6.5% for stage 3 (≥180/110 mm Hg).

PHYSIOLOGICAL CONSIDERATIONS

This high prevalence of hypertension in older persons suggests that the recognition and treatment of hypertension should be a priority for physicians. After a diagnosis is made, based on several readings over time and a persistent BP of 140/90 mm Hg or greater, there are certain factors to be considered prior to instituting any type of therapy. Physiological effects of aging include a decrease in glomerular filtration, cardiac index, and maximal breathing capacity. Metabolism may decrease with changes in hepatic blood flow and reduced hepatic mass, and intestinal absorption is altered by a higher gastric pH, a decreased absorptive surface, a decline in gastrointestinal motility, and reduced splanchnic blood flow. Total body water and lean body mass are reduced, and body fat increases in older individuals. Thus, the volume of distribution of water-soluble drugs may be smaller in the elderly, resulting in higher plasma concentrations. Lipid-soluble drugs have a
greater distribution and a longer elimination time. Theoretically, these alterations in physiology may increase the likelihood of adverse drug reactions in the elderly. Altered drug concentrations, impaired organ functions and response, multiple disease states, increased number of medications, and, perhaps, altered compliance favor the higher likelihood of adverse drug reactions in older persons.

Despite these changes, most elderly patients tolerate medication without a significant increase in adverse events compared with younger patients or control groups. It is important to take a careful drug history (including over-the-counter drugs) and to know the effects aging may have on the medications prescribed; many elderly patients may be taking 2 or 3 drugs in addition to antihypertensive agents. Prescribed and over-the-counter drugs should be reviewed regularly. Fixed-dose combination drugs for hypertension have the potential for simplifying drug therapy and reducing drug costs; this is especially important in the elderly. There is also the possibility of drug-induced illness in elderly patients. For example, anorexia and weight loss might be caused by digitalis intoxication rather than an underlying malignant neoplasm; severe constipation may be secondary to the use of a calcium channel blocker and therefore would not require a workup for an intestinal lesion.

DIAGNOSIS

The diagnosis of hypertension in the elderly presents certain challenges to physicians. Older patients may have rigid arteries as a result of atherosclerosis that increase the measured BP. It may require more pressure in the cuff to obliterate the brachial artery; systolic BP may be recorded at a level higher than the true reading. However, a pulseless, palpable radial artery (Osler sign) that is present after inflation of the BP cuff above the systolic BP is relatively uncommon and is not as reliable an indicator of pseudohypertension as previously thought. In addition, there is increased variability in the measurement of BP in older persons, especially in women. More measurements may be required before concluding that the patient has hypertension. Finally, postural hypotension may occur more commonly among elderly patients. Defining postural hypotension as a decrease in systolic BP of 20 mm Hg or more, the Systolic Hypertension in the Elderly Program (SHEP) observed a prevalence of 10.4% at 1 minute and 12.1% at 3 minutes; however, postural hypotension was present at both 1 and 2 minutes in only 5.3% of the population. It is reasonable to monitor standing BP in elderly patients on a regular basis, especially after initiating specific medical therapy.

Essential hypertension is the most common cause of hypertension in the elderly. However, secondary hypertension is more common in the elderly than in younger patients. Renovascular hypertension is probably the most common cause of secondary hypertension and should be suspected in new-onset hypertension in patients 60 years or older or in those whose blood pressure becomes difficult to control with multiple drug therapy. Excessive ethanol use and nonsteroidal anti-inflammatory drugs are often overlooked as secondary causes of elevated BP in this age group.

### Table 1. Trials Examining Treatment of Hypertension in the Elderly

<table>
<thead>
<tr>
<th></th>
<th>EWPHE (N = 840)</th>
<th>MRC-Elderly (N = 4396)</th>
<th>SHEP (N = 4736)</th>
<th>STOP-H (N = 1627)</th>
<th>Syst-China (N = 2394)</th>
<th>Syst-Eur (N = 4895)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke reduction, %</td>
<td>-36</td>
<td>-25</td>
<td>-33‡</td>
<td>-47†</td>
<td>-38†</td>
<td>-42†</td>
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<tr>
<td>CAD change, %</td>
<td>-20</td>
<td>-19‡</td>
<td>-27†</td>
<td>-13§</td>
<td>+6</td>
<td>-26</td>
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<tr>
<td>CHF reduction, %</td>
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<td>Not stated</td>
<td>-55†</td>
<td>-51†</td>
<td>-58</td>
<td>-27</td>
</tr>
<tr>
<td>% of Patients receiving combination drug therapy</td>
<td>35</td>
<td>52 (β-blocker); 38 (diuretic)</td>
<td>44</td>
<td>67</td>
<td>11-26</td>
<td>26-36</td>
</tr>
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</table>

*EWPHE indicates European Working Party on Hypertension in the Elderly; MRC-Elderly, Medical Research Council Trial in the Elderly; SHEP, Systolic Hypertension in the Elderly Program; STOP-H, Swedish Trial in Old Patients With Hypertension; Syst-China, Systolic Hypertension in China Trial; Syst-Eur, Systolic Hypertension in Europe Trial; CAD, coronary artery disease; and CHF, coronary heart failure.

†P < .01.

‡CAD events were reduced for subjects who were treated with diuretics but not β-blockers.

 §Myocardial infarction only; however, the rate of sudden death was 6.8 vs 2.3 per 1000 patient-years for placebo vs active treatment (relative risk, 0.33).

Randomized hypertension treatment trials in the elderly have documented a 34% reduction in strokes, a 19% reduction in coronary heart disease events, and a 23% reduction in vascular deaths after 5 years of follow-up with a 12- to 14-mm Hg change in systolic BP and a 5- to 6-mm Hg change in diastolic BP compared with placebo or control. In 1985, the European Working Party on Hypertension in the Elderly Trial, a randomized, multicenter, placebo-controlled, double-blind study (N = 840), was the first trial to assess the effects of antihypertensive drug therapy on persons 60 years or older with a systolic BP of 160 to 239 mm Hg and a diastolic BP of 90 to 119 mm Hg. Active therapy with 1 or 2 tablets of hydrochlorothiazide/triamterene (25/50 mg) every day, with the addition of methyldopa (250-2000 mg) in 35% of the subjects, reduced cardiac deaths by 38% (P = .04). During the past 10 years, additional trials have clearly added to our knowledge of the treatment of hypertension of the elderly. It is interesting that it has not been previously emphasized that combinations of drugs have been needed to achieve the reductions in vascular events observed in all of these treatment trials (Table 1).

Medical Research Council Trial in the Elderly

The Medical Research Council Trial in the Elderly (MRC-Elderly) was a randomized, placebo-controlled,
Patients received placebo, amiloride hydrochloride (2.5-5 mg) with hydrochlorothiazide (25-50 mg), or atenolol (50-100 mg). To be eligible for this trial, male and female patients aged 65 to 74 years were required to have a systolic BP between 160 and 209 mm Hg and a diastolic BP of 114 mm Hg or lower. Treatment with diuretics and β-blockers significantly (P = .04) reduced the rate of strokes compared with placebo. Overall coronary events, when the results of both treatments were combined, were not significantly reduced by drug therapy (P = .08). However, treatment with diuretics was superior (P = .006) to β-blocker therapy in reducing coronary events and reduced these events significantly. The benefit of β-blockers in reducing overall cardiovascular events was not seen among smokers, but in nonsmokers the rate (per 1000 patient-years) of cardiovascular events was 19.6 for treatment with β-blockers, 14.3 for treatment with diuretics, and 23.3 for placebo. A combination of drugs was often required to achieve target BP control; 52% of patients who were treated with β-blockers and 38% of patients who were treated with diuretics required additional antihypertensive drugs to achieve a systolic BP goal of 150 to 160 mm Hg.

**Swedish Trial in Old Patients With Hypertension**

The Swedish Trial in Old Patients With Hypertension (STOP-Hypertension) was a multicenter, randomized, double-blind trial involving 927 patients aged 70 to 84 years with either a systolic BP of 180 to 230 mm Hg and a diastolic BP of 90 mm Hg or higher or a diastolic BP of 105 to 120 mm Hg. The primary end points included stroke, myocardial infarction, and cardiovascular deaths. The drugs used could include atenolol (50 mg once daily), hydrochlorothiazide (25 mg once daily) in combination with amiloride (2.5 mg once daily), metoprolol (100 mg once daily), pindolol (5 mg once daily), or placebo. Two thirds of the active patients required a combination of antihypertensive therapy drugs to achieve BP control. A significantly greater percentage of elderly patients (P = .003) receiving active drugs were free of cardiovascular events compared with those receiving placebo over the 4 years of treatment. Although not a primary end point, total mortality was significantly (P = .008) reduced as well.

**Systolic Hypertension in the Elderly Program**

The Systolic Hypertension in the Elderly Program (SHEP) trial was a multicenter, randomized, double-blind, placebo-controlled trial of patients 60 years or older. Subjects received either placebo or chlorthalidone (12.5-25 mg once daily), with either atenolol (25-50 mg once daily) or reserpine (0.05 mg once daily) added, if needed. A reduction of 36% in fatal and nonfatal strokes was achieved compared with patients receiving placebo. There was also a significantly lower rate of nonfatal heart failure and myocardial infarction. To achieve these results, 44% of the subjects received combination drug therapy to attain the target BP goal. Interestingly, subjects receiving active therapy were not more likely to experience faintness on standing, feelings of imbalance, falls, or fractures compared with patients receiving placebo.

Active drug therapy did result in statistically significant (but clinically unimportant) changes in levels of glucose (an increase of 0.3 mmol/L [3.6 mg/dL], P < .01), total cholesterol (an increase of 0.09 mmol/L [3.5 mg/dL], P < .01), creatinine (an increase of 2 μmol/L [0.03 mg/dL], P < .001), triglycerides (an increase of 0.19 mmol/L [17 mg/dL], P < .001), uric acid (an increase of 0.04 mmol/L [0.06 mg/dL], P < .001), and potassium (a decrease of 0.3 mmol/L, P < .001). There was no significant increase of new cases of diabetes mellitus with active therapy compared with placebo (8.6% vs 7.5%, P = .25) after 3 years of treatment. The patients with diabetes who received active treatment in the SHEP cohort experienced the same or a greater reduction in total cardiovascular events than patients without diabetes; their absolute reduction in cardiovascular events was 2 times greater than that of patients without diabetes. The outcome among 1148 patients with hypertension and type 2 diabetes is also consistent with the benefits observed in the United Kingdom Prospective Diabetes Study 39, which documented the equal effectiveness of tight BP control and treatment with either atenolol or captopril in reducing the incidence of diabetic end points of macrovascular (myocardial infarction, sudden death, heart failure, or stroke) and microvascular (retinopathy, albuminuria, or renal failure) complications. Sixty percent of subjects required 2 or more drugs to attain target BP, and tight BP control resulted in a significantly greater reduction in diabetic end points (including death) than less tight control.

Finally, in the SHEP trial, patients with baseline hyperlipidemia also experienced a reduction in coronary heart disease events in this diuretic- and β-blocker–based 5-year trial that was equivalent to that of subjects with normal lipid levels. Importantly, the incidence of dementia or depression was not increased by therapy and BP lowering.

**The Systolic Hypertension in Europe Trial**

The Systolic Hypertension in Europe (Syst-Eur) Trial was a randomized, double-blind placebo trial in pa-
tients 60 years and older with isolated systolic hypertension. Subjects received an immediately long-acting calcium channel blocker (nitrendipine, 10-40 mg once daily), with enalapril maleate (5-20 mg once daily) if needed; this was supplemented with hydrochlorothiazide (12.5-20 mg once daily), if needed, to achieve BP control. The use of combination drug therapy was common to achieve BP control. There was a 42% reduction in fatal and nonfatal strokes for active treatment (n = 2398) compared with placebo (n = 2297). For fatal and nonfatal strokes the reduction was 58% (P = .02). Fatal and nonfatal heart failure was reduced by 58% (P = .13), and fatal and nonfatal myocardial infarction increased by 6% (P = .91); however, cardiac end points occurred at a 52% to 53% lower rate than stroke end points.

**THE SIXTH REPORT OF THE JOINT NATIONAL COMMITTEE ON PREVENTION, DETECTION, EVALUATION, AND TREATMENT OF HIGH BLOOD PRESSURE**

To guide the urgency of treatment, the Sixth Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure has emphasized stratification, according to major risk factors and target organ damage or clinical cardiovascular disease and BP levels. The major risk factors that are considered include smoking, dyslipoproteinemia, diabetes mellitus, older than 60 years or menopausal status, and a family history of premature cardiovascular disease. Target organ damage or clinical cardiovascular disease includes heart diseases (left ventricular hypertrophy, angina or myocardial infarction, coronary revascularization, and congestive heart failure), stroke or transient ischemic attack, nephropathy, peripheral arterial disease, and retinopathy. It is obvious that older persons are more likely to have more risk factors or target organ damage and are at greater risk than younger individuals.

Knowledge of risk factors and target organ damage provides the information to stratify patients with hypertension into 1 of 3 risk groups. Patients in risk group A are classified as having no risk factors or target organ damage other than an elevated BP. Patients in risk group B have 1 other risk factor (but not diabetes mellitus) in addition to hypertension. Risk group C identifies individuals who are at high risk as a result of having target organ damage, clinical cardiovascular disease, or diabetes mellitus alone, or having 2 or more risk factors. Older persons are more likely to fall into risk group C and require initial drug therapy as well as lifestyle interventions, even if they only have stage 1 hypertension (140-159/90-99 mm Hg) and receive treatment for high-normal BP (130-139/85-89 mm Hg) if heart failure, renal insufficiency, or diabetes mellitus is present (Table 2).!

**LIFESTYLE THERAPY**

The Joint National Committee and the Society of Geriatric Cardiology emphasize that lifestyle modifications should be a part of the treatment of hypertension regardless of the age of patients. However, it is often said that elderly patients will not follow lifestyle therapy. Losing weight, limiting alcohol intake, increasing physical activities, and reducing sodium intake are modifications in lifestyle that are recommended. Recently the Trial of Nonpharmacologic Interventions in the Elderly (TONE) documented that lifestyle modification could be achieved in elderly patients. This was a randomized controlled trial of

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### Table 2. Risk Classification and Treatment

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<tr>
<th>Blood Pressure Level (Systolic/Diastolic), mm Hg</th>
<th>Risk Group</th>
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*For heart or kidney failure and diabetes mellitus.
†For patients with multiple risk factors, clinicians should consider drugs as initial therapy with lifestyle therapy.
875 men and women aged 60 to 80 years who had BP lower than 145/85 mm Hg while taking a single anti-hypertensive drug. Patients were randomized to treatment based on their body habitus. Obese patients (n = 585) received either usual care or sodium restriction, a dietary intake of 80 mmol over 24 hours as measured by 24-hour urine sodium collection, a weight loss program to achieve a loss of 4.5 kg, or a combination of sodium restriction and weight loss therapy. Non-obese patients (n = 390) were randomized to either usual care or sodium restriction. After 3 months of nonpharmacological therapy, antihypertensive medication withdrawal was attempted. The sodium restriction group reduced average sodium intake by about 40 mmol/d. In the weight loss group, average body weight decreased by 3.5 kg. After 30 months, 44% of patients in the combined sodium and weight reduction group achieved the primary end point, that is, freedom from recurrence of hypertension or not receiving specific treatment for hypertension or for a cardiovascular event (Figure 1). Compared with 16% in the usual care group, 34% of the sodium restriction group and 37% of the weight reduction group achieved the primary end point at 30 months. This type of intensive intervention is not always possible in the usual care setting, but these study results suggest what can be accomplished.

TREATMENT

For patients without complications, diuretics or β-blockers should be considered for initial therapy. Low doses of medication should be given and slowly titrated. The cardiovascular benefits of β-blockers for elderly patients with hypertension are not as clear as they are for those receiving diuretics. However, data do support the benefits of therapy with β-blockers in reducing both stroke- and heart failure–related events in patients with hypertension and in preventing recurrent myocardial infarctions in both high- and low-risk patients with previous coronary episodes. Many elderly patients fall into this category. The Veterans Affairs Cooperative Study Group on Antihypertensive Agents has documented the ability of β-blocker therapy to lower BP in older patients; results are similar to those achieved with other antihypertensive agents (Figure 2). As noted, most of the trials that documented benefit from BP lowering used a diuretic plus another therapeutic agent in at least 35% of patients. Low-dose combinations have been shown to be well tolerated in elderly patients with hypertension and are associated with a better control rate than monotherapy (Figure 3). When low-dose diuretic combinations are used, the risk of adverse effects is 5% compared with 6% among patients receiving placebo.

The Joint National Committee suggests diuretics or β-blockers as initial therapeutic agents and the use of other antihypertensive agents for specific indications. For systolic heart failure, converting enzyme inhibitors and diuretics are appropriate initial choices. For myocardial infarction, β-blockers without intrinsic sympathomimetic activity are recommended; if systolic dysfunction is also present, then angiotensin-
converting enzyme inhibitors should also be used. If type 1 diabetes with proteinuria is present, angiotensin-converting enzyme inhibitors are indicated. For isolated systolic hypertension (primarily in the elderly), diuretics are preferred, although a long-acting dihydropyridine may be an alternative if diuretics are ineffective or poorly tolerated. Other drugs that can have favorable effects on comorbid diseases are listed in Table 3.

Based on the studies we reviewed, combination therapy may often be necessary to provide additional efficacy in elderly patients. Since the overall national response rate is low (and somewhat lower in 1988-1991), it may be that more patients in this age group should be receiving this type of therapy. The control rate for men 70 years and older varies from 16% to 29% (Figure 4). Fixed-dose combination antihypertensive drugs can simplify dosing regimens, improve compliance, improve BP control, decrease dose-dependent adverse effects, and reduce cost. Therefore, this approach to therapy may be advantageous to elderly subjects. Moreover, a Veterans Affairs Study indicated that combinations of antihypertensive drugs that included a diuretic were more effective than a combination that did not.

CONCLUSIONS

In summary, the treatment of hypertension in older persons requires consideration of not only altered drug metabolism but also special physiological considerations, including postural hypotension, a decrease in cardiac output, plasma volume, renal function, and possibly altered mental capacity. The treatment trials of hypertension in the elderly have been successful in...
REFERENCES

1. The Sixth Report of the Joint National Commit-
tee on Prevention, Detection, Evaluation, and Treat-
ment of High Blood Pressure [published correc-


3. National High Blood Pressure Education Pro-
gram Working Group. National High Blood Pres-

4. Montamat SC, Cusack BJ, Vestal RE. Manage-

5. Borhani NO. Prevalence and prognostic signifi-
cance of hypertension in the elderly. J Am Geri-
atr Soc. 1986;34:112-114.

6. Gurland BJ, Teresi J, Smith WM, Black D, Hughes G, Edlavitch S. Effects of treatment for isolated sys-
tolic hypertension on cognitive status and depres-


9. Messerli FH, Grossman E, Goldbourt U. Are beta-
blockers efficacious as first-line therapy for hy-

lis R. Osler’s maneuver: absence of usefulness for the detection of pseudohypertension in an el-

11. Messerli FH, Osler’s maneuver, pseudohyperten-


13. Applegate WB, Davis BR, Black HR, Smith WM, Miller ST, Burlando AJ. Prevalence of postural hy-
potension at baseline in the Systolic Hyperten-

14. MacMahon S, Rodgers A. The effects of blood pressure reduction in older patients: an overview of five randomized controlled trials in elderly hyperten-

15. Arteries, Birkenhäuser W, Brixio P, et al. Mortal-
ity and morbidity results from the European Work-

16. MacMahon S, Rodgers A. The effects of blood pressure reduction in older patients: an overview of five randomized controlled trials in elderly hyperten-


ity and morbidity results from the European Work-

18. Dahlof B, Lindholm LH, Hansson L, Scherstén B, Ekborn T, Waster PO. Morbidity and mortality in the Swedish Trial in Old Elderly with Hyperten-

19. Kannel WB. Role of blood pressure in cardiovas-


tolic Hypertension in Europe (Syst-Eur) Trial In-
vestigators. Randomised double-blind compari-

22. Liu L, Wang J, Davis B, Liu G, Staessen JA, for the Systolic Hypertension in China (Syst-China) Collaborative Group. Comparison of active treat-


term, low-dose, diuretic-based, antihypertensive therapy on glucose, lipid, uric acid, and potas-
sium levels in older men and women with iso-
lated systolic hypertension: the Systolic Hyper-

25. Curb JD, Pressel SL, Cutler JA, et al. for the Sys-
tolic Hypertension in the Elderly Program Coop-
erative Research Group. Effect of diuretic-based antihypertensive treatment on cardiovascular dis-
ase risk in older diabetic patients with isolated systolic hypertension [published correction ap-

26. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complica-


28. Moser M, Chetlin MD, Gifford R. Treatment of high blood pressure: a position paper from the Soci-

29. Of Antihypertensive and Diuretic Agents. Randomized con-
trolled Trial of atenolol and placebo in the Elderly (TONE). JAMA. 1998;279:839-
846.

30. Messerli FH, Grossman E, Goldbourt U. Are beta-
blockers efficacious as first-line therapy for hy-

31. Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive thera-
pies used as first-line agents: a systematic re-
view and meta-analysis. JAMA. 1997;279:737-
745.

32. Krumholz HM, Radford MJ, Wang Y, Chen J, He-
it A, Marciniak TA. National use and effective-
ness of beta-blockers for the treatment of elderly patients after acute myocardial infarction: Na-
tional Cooperative Cardiovascular Project [pub-
lished corrections appear in JAMA. 1999;281:

33. Materson BJ, Reda DJ, Cushman WC, et al, for the Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Single-

drug therapy for hypertension in men: a compari-


35. Prisant LM, Doll NC. Hypertension: the rediscov-

36. Frishman WH, Burris JF, Mrozcek WJ, et al. First-
line therapy option with low-dose bisoprolol fu-
marate and low-dose hydrochlorothiazide in pa-
tients with stage I and stage II systemic hyperten-

37. Burris JF, Mrozcek WJ. A first-line treatment op-
tion for elderly hypertensive patients: a low-dose multimechanism β-blocker/diuretic. Am J Geri-

38. Neutel JM. Metabolic manifestations of low-
715-825.

39. Neutel JM, Rolf CN, Valentine SN, Li J, Lucas C, Marmorstein BL. Low-dose combination therapy as first line treatment of mild-to-moderate hyper-

40. Materson BJ, Reda DJ, Cushman WC, Hender-
son WG, for the Department of Veterans Affairs Cooperative Study Group on Antihyperten-
sive Agents. Results of combination anti-hyperten-
sive therapy after failure of each of the compo-