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Selection of Initial Antihypertensive Therapy, Regimen Design, and Goal Blood Pressure

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No Blood Pressure Reduction is Trivial

Systolic and diastolic blood pressures (BPs) have a strong, continuous, graded, and etiologically significant positive association with cardiovascular disease outcomes. Small reductions in systolic and diastolic BP lead to large and proportionate reductions in ischemic heart disease, stroke, and vascular mortality. A recently reported meta-analysis of nearly a million people without pre-existing vascular disease and participating in clinical trials or observational studies analyzed the relationship between BP and cardiovascular mortality (1). A steep, direct log-linear relationship between systolic and diastolic BP was seen with mortality caused by stroke, ischemic heart disease, and other vascular diseases, including heart failure. The dose-response relationship is seen continuously until 89 years of age. Thus, even the very old have the same relationship between BP and vascular mortality.

The million people meta-analysis also was unable to find a threshold at which BP reduction does not yield benefit. The lowest usual BP at any age associated with the best outcomes was 115/75 mmHg. The proportionality of risk reduction also reveals that 20 mmHg systolic BP reduction from 130 to 110 mmHg translates to the same risk reduction as from 180 to 160 mmHg. Vasan et al. (2) analyzed the relationship of high-normal BP with cardiovascular outcomes in men and women in the Framingham cohort. Four BP categories—optimal, normal, high-normal, and hypertension—were studied as defined by the Sixth Joint National Committee. High-normal BP was associated with increased cardiovascular events in both men and women. Even after adjusting for other cardiovascular risk factors (age, body mass index, total cholesterol, diabetes, smoking, and examination year), the risk of first major cardiovascular event was increased 40% in women and 20% in men per change in BP category. A continuous trend for cardiovascular disease across the 3 nonhypertensive BP categories was seen. The authors conclude, "A 20% overall absolute risk of CV events at 10 years currently defines the threshold for treatment of hypertension. In subjects >65 years age, the 10-year absolute risk exceeded 20% in men and approached this in women. Assuming a 25% risk reduction, the estimated number needed to treat over 5 years would be 28 men or 41 women."

These data show that no BP reduction is trivial, and the risk reduction is log-linear. Thus, if the baseline absolute risk is high, the reduction in BP needed to reduce cardiovascular outcomes will be evident with a smaller number of patients.

Diuretics and Beta-blockers Are Underused

Use of older antihypertensive drugs is declining. In the Cardiovascular Health Study, a prospective community-based cohort study of risk factors for coronary heart disease (CHD) and stroke in people 65 years and older, initiated in June 1990, the time trends of use of antihypertensive drugs were examined. Among those free of coronary artery disease, the use of thiazide diuretics dropped markedly, from 60% in 1990 to 38% in 1999, whereas use of ACE inhibitors doubled from 17% to 37% and calcium channel blockers increased from 14% to 35%. In those with coronary artery disease, the patterns were different. Thiazide diuretic use declined from 36% to 19%, and the use of loop diuretics increased from 19% to 30%. Beta-blocker use first declined to 32% in

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1993 and then increased to 41% in 1999. Angiotensin-converting enzyme (ACE) inhibitor use increased linearly from 18% to 40%, and calcium-channel blocker use increased to a peak of 57% in 1994 and then declined to 43%. The authors attribute the time trends in drug use to advertising trends, not a wealth of evidence-based trials supporting the use of newer drugs, especially calcium-channel blockers.

In the context of these trends, and debate about the efficacy of the newer drugs, especially at an increased cost, data are needed to justify the use of newer antihypertensive agents compared with older drugs.

Thiazide Diuretics Are Safe and Effective

Psaty et al. (3) reported a meta-analysis of long-term placebo-controlled randomized trials that assessed major disease outcomes. The safety and efficacy of various antihypertensive therapies used as first-line agents were tested. Diuretics and beta-blockers were evaluated in 18 long-term randomized trials. Compared with placebo, beta-blocker therapy was effective in preventing stroke (risk ratio [RR], 0.71; 95% confidence interval [CI], 0.59–0.86) and congestive heart failure (RR, 0.58; 95% CI, 0.40–0.84). The findings were similar for high-dose diuretic therapy (for stroke, RR, 0.49; 95% CI, 0.39–0.62; and for congestive heart failure, RR, 0.17; 95% CI, 0.07–0.41). Low-dose diuretic therapy prevented not only stroke (RR, 0.66; 95% CI, 0.55–0.78) and congestive heart failure (RR, 0.58; 95% CI, 0.44–0.76) but also coronary disease (RR, 0.72; 95% CI, 0.61–0.85) and total mortality (RR, 0.90; 95% CI, 0.81–0.99).

Since the publication of this meta-analysis in 1997, several additional studies have supported the use of older agents and are discussed further.

Swedish Trial in Old Patients with Hypertension-2 (STOP-2)

The primary objective of this randomized, controlled, open-label trial was to compare cardiovascular mortality and morbidity in elderly patients with hypertension (4). A total of 6614 patients age 70 to 84 years with BP 180 mmHg or higher systolic or 105 mmHg or higher diastolic were randomly assigned conventional antihypertensive drugs (atenolol 50 mg, metoprolol 100 mg, pindolol 5 mg, or hydrochlorothiazide 25 mg plus amiloride 2.5 mg daily) or newer drugs (enalapril 10 mg, lisinopril 10 mg, felodipine 2.5 mg, or isradipine 2–5 mg daily). Fatal stroke, fatal myocardial infarction, and other fatal cardiovascular disease were analyzed by intention to treat. BP was decreased similarly in all treatment groups. The incidence of the primary combined end-point of fatal stroke, fatal myocardial infarction, and other fatal cardiovascular disease was 19.8 events per 1000 patient-years with both conventional and newer drugs. The combined end-point of fatal and nonfatal stroke, fatal and nonfatal myocardial infarction, and other cardiovascular mortality occurred in 460 patients taking conventional drugs and in 887 taking newer drugs (0.96 [0.86–1.08], $p = 0.49$). Thus, older (diuretics and beta-blockers) and newer (ACE inhibitors and calcium channel blockers) antihypertensive drugs were similar in prevention of cardiovascular mortality or major events.

Antihypertensive and Lipid-lowering Therapy to Reduce Heart-attack Trial (ALLHAT) Trial

The ALLHAT trial is the largest outcome trial comparing an older agent-based therapy (chlorthalidone) with 3 newer agents (alpha-blocker, ACE inhibitor, calcium-channel blocker). The primary objective of the ALLHAT trial was to compare the effect of diuretic-based therapy (chlorthalidone) with newer agents—doxazosin, lisinopril, and amlodipine—on the incidence of cardiovascular disease in patients with high-risk hypertension (5,6). To enter the trial, subjects had to be 55 years or older and have hypertension (systolic BP of 140 or higher or diastolic BP of 90 or higher or taking antihypertensive medications). They also had to have at least 1 coronary risk factor—previous myocardial infarction or stroke, left ventricular hypertrophy (LVH) (by electrocardiogram or echocardiogram), type 2 diabetes mellitus, current smoking, or low high-density lipoprotein (HDL). A total of 33,357 subjects were randomized, and the primary end-point was fatal CHD or nonfatal myocardial infarction analyzed by intention to treat analysis. Secondary end-points included all-cause mortality, stroke, combined CHD (primary end-point plus hospitalized angina or coronary revascularization and combined cardiovascular disease). Combined cardiovascular disease was defined as combined CHD plus treated as outpatient angina, congestive heart failure (hospitalized or outpatient), and peripheral arterial disease (in-hospital or outpatient revascularization). The trial was a double-blind, randomized, large sample trial with 1.7:1:1:1 assignment to chlorthali-

done:doxazosin:lisinopril:amlodipine and a planned follow-up of 4 to 8 years in 623 centers in the United States and Canada. Chlorthalidone was used in the dose of 12.5 to 25 mg/d (n = 15255), doxazosin 2 to 8 mg/d (n = 9067), lisinopril 10 to 40 mg/d (n = 9054), and amlodipine 2.5 to 10 mg/d (n = 9048). Those with history of hospitalized or treated symptomatic heart failure or known ejection fraction less than 0.35 were excluded.

The protocol specified a goal diastolic BP lower than 90 and systolic BP lower than 140 with the lowest dose of the randomly assigned drug, with 3 titration steps to achieve goal BP. Thereafter, a step-care protocol with an open-label drug was followed. Step 2 agents were atenolol 25 to 100 mg/d, reserpine 0.05 to 0.2 mg/d, and clonidine 0.1 to 0.3 mg twice a day, and the step 3 agent was hydralazine 25 to 100 mg twice a day.

Mean age was 67 years, 47% were women, and 32% were black. Ninety percent were previously treated hypertensives. The qualifying high-risk state was equally distributed among the classes of drugs: 22% smokers, 36% diabetics, 12% low HDL cholesterol, 21% LVH, and 52% atherosclerotic cardiovascular disease. No washout or placebo run-in was used, and BP at entry was 146/84 mmHg in all groups.

The doxazosin arm of the trial was stopped early because of 25% higher risk of combined cardiovascular end-points in the doxazosin group and a less than 1% chance of finding a significant beneficial effect of doxazosin by 16% over chlorthalidone by the end of the trial (5). Systolic BP achieved in the doxazosin group was 2 mmHg higher at 4 years compared with chlorthalidone. Goal BP was achieved in 64% of the chlorthalidone arm vs 58% of the doxazosin arm at 4 years. The risk ratios for the doxazosin-treated group compared with the chlorthalidone-treated group were 1.19 for stroke, 1.25 for combined cardiovascular disease (CVD), 2.04 for heart failure, 1.16 for hospitalized angina, and 1.15 for coronary revascularization.

Could the poorer control of BP in the doxazosin arm account for the poorer outcomes? In the SHEP trial, a 12 mmHg reduction in systolic BP caused a 49% reduction in heart failure. Thus, a 10% to 20% increase in the risk of heart failure with a 3 mmHg systolic BP difference is possible, but not doubling of the risk. However, BP differences can account for a 15% to 20% increase in stroke risk and a 12% increase in angina risk, which is what was observed.

Why did alpha-blockers produce more heart failure? Diuretics when compared with alpha-blockers produce a greater reduction in LVH, and this may account for the greater reduction in comparative trials (7). The authors conclude that mechanistic evidence is nonconclusive as to the biologic plausibility of these findings.

The mean follow-up in the overall study without doxazosin was 4.9 years. Those on chlorthalidone experienced the best BP reduction. Compared with the chlorthalidone group, the lisinopril group had 2 mmHg higher systolic and approximately 1 mmHg higher diastolic BP, whereas the amlodipine group had 0.8 mmHg higher systolic but 0.8 mmHg lower diastolic BP. Goal BP was achieved in 68% of the chlorthalidone arm vs 66% of the amlodipine arm (p = NS) vs 61% of the lisinopril arm ($p < 0.001$) at 5 years. The achieved BP goal was between 51% and 61% in the lisinopril group compared with 58% to 68% of the diuretic group, with the differences statistically different in each of the 5 years. Whereas the diuretic and amlodipine group needed 1.4 to 1.9 medications to improve BP control, those on lisinopril needed 1.5 to 2 medications. Step 2 and 3 drug use in the nonlisinopril groups was between 25% and 41%, and in the lisinopril group, between 33% and 43% to achieve the goal. Of the patients who stopped medication, elevated BP was the cause in 4.5%, 3.5%, and 9.0%, respectively, in the chlorthalidone, amlodipine, and lisinopril groups.

Cholesterol levels were higher and the incidence of hypokalemia and new onset diabetes mellitus more common with the chlorthalidone groups compared with other groups at 2 and 4 years of follow-up.

The risk ratios for primary outcome or total mortality were no different among the 3 drugs. For amlodipine vs chlorthalidone, secondary outcomes were similar, except for a higher 6-year rate of heart failure with amlodipine (10.2% vs 7.7%; RR, 1.38). For lisinopril vs chlorthalidone, lisinopril had higher 6-year rates of combined CVD (33.3% vs 30.9%; RR, 1.10), stroke (6.3% vs 5.6%; RR, 1.15) and heart failure (8.7% vs 7.7%; RR, 1.15).

Could the poorer control of BP in the lisinopril arm account for the poorer outcomes? The authors conclude that a 2 to 3 mmHg difference in BP might account for a 6% to 12% difference in stroke rates and a 10% to 20% higher risk of heart failure seen in the lisinopril group. Accordingly, lisinopril was as good as diuretics.

The trial demonstrates the importance of reaching goal BP. The diuretic-based antihypertensive drug regimen lowers BP more and therefore provides cardiovascular protection. Thiazide-type diuretics are inexpensive and should be an essential part of any multidrug antihypertensive regimen.

Two other trials also show the value of diuretics in antihypertensive drug therapy.

Intervention as a Goal in Hypertension Treatment (INSIGHT)

This study asked the following question: does long-acting nifedipine reduce cardiovascular morbidity and mortality in a high-risk hypertensive population compared with diuretic-based therapy? (8) The primary end-points were cardiovascular deaths, strokes, myocardial infarctions, and congestive heart failure. A total of 3157 patients received nifedipine and 3164 patients a hydrochlorothiazide/amiloride combination. A stepped care approach was used to reduce BP to less than 140/90 mmHg or to produce a fall of at least 20/10 mmHg. The rate of primary outcome overall was 18.2 events/1000 patient-years in the nifedipine group and 16.5/1000 patient-years in the diuretic group (RR, 1.11; $p = 0.34$). Thus, the diuretic-based regimen compared favorably with a calcium-channel blocker-based regimen.

Nordic Diltiazem Study (NORDIL)

NORDIL evaluated the role of diltiazem compared with older antihypertensive drugs—diuretics or beta-blockers—in reducing cardiovascular morbidity and mortality (9). It was an open-label, prospective, randomized study with blinded evaluation of end-points in 5410 patients receiving diltiazem and 5471 patients receiving older antihypertensive drugs (diuretics, beta-blockers, or both). A step-care approach was used to reduce diastolic BP to lower than 90 mmHg. The combined primary end-point was fatal and nonfatal stroke, myocardial infarction, and other cardiovascular death. Systolic and diastolic BP were lowered effectively in the diltiazem and diuretic and beta-blocker groups (reduction 20.3/18.7 mmHg vs 23.3/18.7 mmHg; difference in systolic reduction $p < 0.001$). RR for primary end-point in the diltiazem group compared with conventional agents was 1.0 (16.6 vs 16.2 events per 1000 patient-years, $p = 0.97$). RR for fatal and nonfatal stroke was 0.80 (6.4 vs 7.9 events per 1000 patient-years, $p = 0.04$) and for fatal and nonfatal myocardial infarction was 1.16 (7.4 vs 6.3 events per 1000 patient-years, $p = 0.17$). Therefore, diuretics, beta-blockers, or both were as effective as diltiazem in preventing the combined primary end-point of all strokes, myocardial infarction, and other cardiovascular death. However, diltiazem provided superior protection from strokes despite poorer systolic BP control.

Case for Angiotensin-converting Enzyme Inhibitors and Angiotensin Receptor Blockers

A few trials have specifically compared ACE inhibitors or angiotensin receptor blockers with conventional therapy and are discussed further.

Captopril Prevention Project (CAPPP) Randomized Trial

In the CAPPP trial, 10,985 hypertensive patients were enrolled to either the ACE inhibitor, captopril (50 mg in 1 or 2 divided doses), or conventional therapy (thiazides or beta-blockers) to compare their efficacy in preventing myocardial infarctions, strokes, or cardiovascular deaths (10). Eligible patients had to have a diastolic BP of 100 mmHg or higher on 2 occasions, and a step-care approach was used to reduce this pressure to 90 mmHg or more. In the overall trial, there was no difference between the 2 treatments in the primary outcome except in those with diabetes mellitus. Patients age 25 to 66 years with a measured diastolic BP of 100 mmHg or higher on 2 occasions were randomly assigned captopril or conventional antihypertensive treatment (diuretics, beta-blockers). The primary end-point was a composite of fatal and nonfatal myocardial infarction, stroke, and other cardiovascular deaths. Of 5492 patients assigned captopril and 5493 assigned conventional therapy, primary end-point events occurred in 363 patients in the captopril group (11.1 per 1000 patient-years) and 335 in the conventional-treatment group (10.2 per 1000 patient-years; RR, 1.05; 95% CI, 0.90–1.22; $p = 0.52$). The individual components of the composite end-points showed heterogeneity. Cardiovascular mortality was lower with captopril than with conventional treatment (76 vs 95 events; RR, 0.77; 95% CI, 0.57- 1.04; $p = 0.092$), and the rate of fatal and nonfatal myocardial infarction was similar (162 vs 161), but fatal and nonfatal stroke was more common with captopril (189 vs 148; RR, 1.25; 95% CI, 1.01–1.55; $p = 0.044$). Thus, captopril and conventional treatment did not differ in efficacy in preventing cardiovascular morbidity and mortality. The authors concluded that the

difference in stroke risk is probably caused by the lower levels of BP obtained initially in previously treated patients randomized to conventional therapy.

Australian National Blood Pressure Study 2 (ANBP2)

An open-label prospective study with blinded assessment of end-points in 6083 relatively healthy elderly subjects with hypertension was performed in 1594 family practices in Australia (11). Ninety-five percent of the subjects were white and had little vascular disease. Although the study was randomized, the family practitioner decided the dose and nature of initial therapy, which was enalapril-based or hydrochlorothiazide-based. Subjects were followed for a median of 4.1 year, and the total numbers of cardiovascular events in the 2 treatment groups were compared. By the end of the study, BP had decreased to a similar extent in both groups (a decrease of 26/12 mmHg), but the hazard ratio for a cardiovascular event or death with ACE inhibitor treatment was 0.89 (95% CI, 0.79–1.00; $p = 0.05$) compared with the diuretic. Men benefited from ACE inhibitors, but women did not. This finding contrasts with the analysis in the larger ALLHAT trial. The rates of nonfatal cardiovascular events and myocardial infarctions decreased with ACE inhibitor treatment, whereas a similar number of strokes occurred in each group (although there were more fatal strokes in the ACE inhibitor group). The authors concluded, "Initiation of antihypertensive treatment involving ACE inhibitors in older subjects, particularly men, appears to lead to better outcomes than treatment with diuretic agents, despite similar reductions of blood pressure."

Use of Angiotensin-converting Enzyme Inhibitors in Black Patients

One troubling observation in ALLHAT trial was that black patients (who constituted 32% of the participants) did not derive as much benefit from lisinopril compared with chlorthalidone. Tests of heterogeneity to measure interaction by race were significant for stroke and combined CVD ($p = 0.01$ and $p = 0.04$ for interaction, respectively). The RRs (lisinopril vs chlorthalidone) were 1.40 and 1.00 for stroke, 1.19 and 1.06 for combined CVD, and 1.32 and 1.15 for heart failure in black and nonblack patients, respectively. Although mean follow-up systolic BP was 4 mmHg higher for black patients (compared with 2 mmHg for all participants), adjusting for the BP difference did not account for the 40% higher risk of stroke, 19% higher risk of combined CVD, and 32% higher risk of heart failure in black patients (Fig 1).

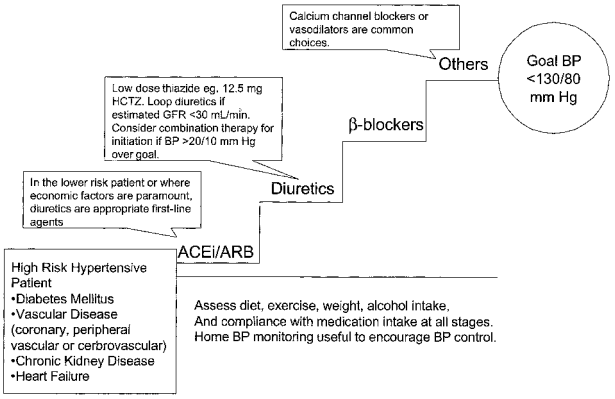

Figure 1. An approach to treat the high-risk patient with hypertension. ACEi, angiotension converting enzyme inhibitor; ARB, angiotension II receptor blocker

There is some support from other trials for these findings of lesser response to ACE inhibitors in black patients. Exner et al. (12) pooled and analyzed data from the Studies of Left Ventricular Dysfunction (SOLVD) prevention and treatment trials, 2 large, randomized trials comparing enalapril with placebo in patients with left ventricular dysfunction. A matched cohort design was used, and a total of 1196 white patients were matched with 800 black patients and followed for an average of 33 to 35 months. Black patients and the matched white patients had similar clinical characteristics, but the black patients had higher rates of death from any cause (12.2 vs 9.7 per 100 person-years) and of hospitalization for heart failure (13.2 vs 7.7 per 100 person-years). Despite similar doses of drugs in the 2 groups, enalapril therapy, as compared with placebo, was associated with a 44% reduction in the risk of hospitalization for heart failure among the white patients ($p < 0.001$) but no significant reduction among black patients ($p = 0.74$). At 1 year, enalapril therapy was associated with significant reductions from baseline in systolic BP of 5.0 mmHg and diastolic BP of 3.6 mmHg among the white patients, but not among the black patients.

Another line of evidence regarding hypertension in black patients comes from the *L*osartan *I*ntervention *f*or *E*ndpoint reduction in hypertension (LIFE) study, a multinational, double-blind, parallel, randomized, active-control study of 9193 patients (13). The trial evaluated the long-term effects of a losartan-based regimen compared with an atenolol-based regimen in patients with documented LVH (determined by electrocardiogram)

on the combination of cardiovascular morbidity (stroke and myocardial infarction) and cardiovascular mortality. It was conducted at 945 sites in 7 countries, enrolling 9193 patients, of whom 1096 patients had a primary end-point with a mean follow-up of 4.8 years. The study was specifically designed to obtain comparable BP control (to <140/90 mmHg) in the 2 treatment groups so that the results would reflect the differences in the mechanisms rather than the magnitude of BP reduction. Diuretics were used with atenolol or losartan 71% of the time.

Data submitted to the US Food and Drug Administration (FDA) by Merck and Co. to seek a new indication for losartan, to reduce cardiovascular morbidity and mortality in hypertensive patients with LVH, analyzes the subgroup of black participants compared with nonblack participants (14). In this trial, 270 black patients were assigned to the losartan group and 263 to the atenolol group. Post hoc analyses revealed a significant qualitative treatment interaction for black patients vs nonblack patients. Nonblack patients appeared to have a lower risk of experiencing an event with losartan, whereas black patients, accounting for 6% of the study population, appeared to have a lower risk with atenolol despite comparable BP reduction. Although there was not a statistically significant effect of ethnic background on the risk of an event in the prespecified groups, there was a suggestion of interaction between ethnic background and treatment (p = 0.057). White patients appeared to have a lower risk with losartan (hazard ratio, 0.819; 95% CI, 0.724–0.928), whereas black patients appeared to have a lower risk with atenolol (hazard ratio, 1.598; 95% CI, 1.004–2.543). A further exploratory analysis dichotomizing patients into black (n = 533) and nonblack (n = 8660) groups yielded a statistically significant interaction (p = 0.005). Further, a test for qualitative interaction (ie, effect of losartan differs in direction between black and nonblack patients, not just in magnitude) was also statistically significant (p = 0.016). Because of the robustness of the dichotomized treatment-by-ethnicity interaction and its qualitative nature (rarely observed in clinical trials), additional exploratory analyses were performed in these 2 groups to evaluate the possible biologic explanations for this finding. Additional analyses of changes in BP, LVH, and heart rate demonstrated that black and nonblack patients behaved similarly in their responses to treatment and therefore did not reveal a biologic basis for the observed interaction with treatment in black and nonblack patients for the primary end-point. However, as indicated by the p value for the test of interaction (p = 0.005) between treatment and the dichotomized groups (black and nonblack), this interaction is unlikely to have occurred by chance. Thus, the benefits of losartan vs atenolol demonstrated in the LIFE study overall do not appear to apply to black patients with hypertension and LVH.

As a note of caution, all these analyses (including ALLHAT) are post hoc. A prospective, double-blind, randomized, 3 × 2 factorial trial in hypertensive black patients with hypertensive kidney disease, the *A*frican-*A*merican *S*tudy of *K*idney Disease and Hypertension (AASK) trial, was recently reported (15). The study compared the effects of 2 levels of BP control (mean arterial pressure of 102–107 mmHg [usual, n = 554] or 92 mmHg or less [lower, n = 540]) and 3 antihypertensive drug classes (beta-blocker, ACE inhibitor, and dihydropyridine calcium-channel blocker) on glomerular filtration rate (GFR) decline in hypertension. A total of 1094 black patients age 18 to 70 years with hypertensive renal disease (GFR, 20–65 mL/min/1.73 m^2) were followed up for 3 to 6.4 years. Initial treatment with metoprolol 50 to 200 mg/d (n = 441), ramipril 2.5 to 10 mg/d (n = 436), or amlodipine 5 to 10 mg/d (n = 217) was randomly assigned. Open-label agents, with loop diuretics as first add-on, were prescribed to achieve the assigned BP goals. Loop diuretics were used 71% to 76% of the time. The primary end-point—GFR event, end-stage renal disease, or death–was 22% lower in the ramipril group compared with the metoprolol group (95% CI, 1–38%, p = 0.04) and not different between the amlodipine and the metoprolol groups. The rate of decline in GFR as measured by the slope of the GFR from the beginning to the end of the trial was slowed 0.61 mL/min/1.73 m^2 in the ramipril group compared with the metoprolol group. No differences in cardiovascular outcomes or total mortality were seen among the 3 classes. Thus, ACE inhibitor-based therapy, especially when used with loop diuretics, in black patients with hypertensive kidney disease appears more effective than beta-blockers or dihydropyridine calcium-channel blockers in slowing GFR decline.

Angiotensin-converting Enzyme Inhibitors Are Also an Excellent Choice When Used with Diuretics

There are several examples of ACE inhibitor-based therapy in which ACE inhibitors were

found to be superior. For example, the *A*ppropriate *B*P *C*ontrol in *D*iabetes (ABCD) trial was a single-center, randomized, controlled trial comparing the effects of moderate control of BP (80–89 mmHg) with those of intensive control (target DBP, <75 mmHg) on the incidence and progression of complications of diabetes (16). Diuretics were used to control BP if the study drug was not sufficient. In each of the 2 groups, patients received enalapril or nisoldipine, a long-acting dihydropyridine calcium-channel blocker. A total of 470 patients participated in the trial, and the primary end-point was the rate of change of creatinine clearance measured every 6 months. Cardiovascular end-points were secondary outcomes. The trial was halted early at 67 months by the Data and Safety Monitoring Committee, who observed a significant difference in the rate of cardiovascular events between the subgroups of patients treated with the study drugs in the hypertensive cohort of the study. Patients had almost identical control of BP, diabetes, and lipids through the 5 years of the study; however, 25 myocardial infarctions were seen in the nisoldipine group and 5 in the enalapril group. The RR was 5.5 (95% CI, 2.1–14.6) and 7.0 after adjustment for baseline variables. The study demonstrates the cardiovascular protection afforded by ACE inhibitors in hypertensive diabetic patients, usually in combination with diuretics, when compared with a long-acting calcium-channel blocker.

The largest experience with an ACE inhibitor has come from the Heart Outcomes Prevention Evaluation (HOPE) study (17). In this trial, 9297 patients older than 55 years with cardiovascular disease or type 2 diabetes were randomized to receive either ramipril or placebo for a mean of 5 years. Patients with diabetes had at least 1 other cardiovascular risk factor, which included hypertension, high total cholesterol, low HDL levels, cigarette smoking, or documented microalbuminuria. Ramipril was started in a dose of 2.5 mg/d for the first week and 5 mg/d for the next 3 weeks, then escalated to a dose of 10 mg/d. ACE inhibitor therapy resulted in overall reduction in the rates of death, myocardial infarction, and strokes by 22%, the primary end-point of the study. The subgroup of patients with diabetes had at least as much benefit in reduction of cardiovascular events and deaths as those without diabetes. This trial demonstrates that ACE inhibitors effectively reduce outcomes in a high-risk population with hypertension. However, the ACE inhibitor group had a mean of 3/2 mmHg lower BP. Furthermore, BP measurements were not at the end of the dosing interval (trough BP) but were made in the morning after administering the medication at night according to the HOPE protocol; thus, the 24-hour reduction of BP may be underestimated based on office BP. In a substudy, 38 patients with peripheral arterial disease underwent 24-hour ambulatory BP (ABP) measurement before randomization and after 1 year (18). Ramipril did not significantly reduce office BP (8/2 mmHg, p = NS) or day ABP (6/2 mmHg, p = NS) after 1 year. However, 24-hour ABP was significantly reduced (10/4 mmHg, $p = 0.03$), mainly because of a more pronounced BP lowering effect during nighttime (17/8 mmHg, $p < 0.001$). The night to day ratio was also significantly lowered in the ramipril group. ABP showed greater falls, especially at night, than office BP during treatment with ramipril given once daily at bedtime. Therefore, the effects on cardiovascular morbidity and mortality seen with ramipril in the HOPE study may, to a larger extent than previously ascribed, relate to effects of BP lowering and nocturnal dipping.

Although calcium-channel blockers were associated with increased cardiovascular events, this finding was not duplicated in the current trial. Nevertheless, the 38% higher risk of heart failure in the calcium-channel blocker group cannot be explained on the basis of BP alone. Even if chlorthalidone treated heart failure before it developed, the 38% higher risk (compared with only a 20% higher risk with lisinopril despite poorer BP control) cannot be explained. Thus, calcium-channel blockers should remain third-line agents in the absence of compelling indications.

Is Initial Therapy More Important Than the Regimen?

ALLHAT compared 3 therapies anchored on drugs from different classes to control hypertension. The second-line agents were adrenergic blockers, which would be a reasonable second choice for those on diuretics and dihydropyridine calcium-channel blockers. However, they would not be the usual drugs to use in patients on ACE inhibitors, for whom diuretics would be a better option. Therefore, those with low renin hypertension such as black patients would have a better response to the diuretic-CCB regimen in ALLHAT, but not ACE inhibitors. Thus, the comparison ALLHAT made tested 2 appropriate regimens (chlorthalidone-based and CCB-based) with a

poor one (lisinopril-based). Although adrenergic blockade is appropriate as a second-line agent in the patients treated with diuretics and CCBs, these agents are not appropriate second-line agents in a setting of ACE inhibition. Diuretics or CCBs would be synergistic with lisinopril. The higher average BP in the lisinopril-based regimen (especially in black patients and elderly patients, in whom the regimen is more likely to fail), with fewer patients at goal BP despite greater use of step 2 and 3 drugs, is evidence that this regimen was not as effective. Furthermore, whereas only 4.5% of the chlorthalidone participants and 3.8% of the amlodipine participants discontinued the study drug because of elevated BP, 9% of the lisinopril participants did. The conclusion that we can draw is that this unusual lisinopril regimen was not as effective as the other regimens.

In contrast with ALLHAT, the LIFE study compared 2 initial therapies, losartan-based or atenolol-based, in controlling strokes, myocardial infarctions, or cardiovascular deaths in hypertensive patients with LVH (13). This trial used low-dose diuretics as second-line agents, and other agents, not including ACE inhibitors, beta-blockers or angiotensin II receptor blockers, as additional add-ons. The use of diuretics as second-line agents in combination with either beta-blockers or angiotensin II receptor blockers is appropriate and does not favor any regimen. The number of agents used to reach goal BP, the proportion of patients who achieved goal BP, and the percent of time patients were on diuretics were nearly identical. Although systolic BP was slightly lower in the losartan group, diastolic BP was slightly higher. Adjustment for BP did not influence the overall results.

Is Initial Therapy More Important Than Reaching Goal Blood Pressure?

Benetos et al. (19) assessed the cardiovascular risk in hypertensive subjects according to systolic and diastolic BP control. Hypertensive French men (n = 4714) treated by their physicians had a standard health checkup at the d'Investigations Preventives et Cliniques Center, Paris, France, between 1972 and 1988 and were prospectively followed for cardiovascular and CHD mortality. They were assessed for a mean period of 14 years. Among treated subjects, 85.5% presented uncontrolled values for systolic BP (≥140 mmHg), diastolic BP (≥90 mmHg), or both. After adjustment for age and associated risk factors (diabetes, smoking, and total cholesterol), these subjects presented an increased risk for CVD mortality (RR, 1.66; 95% CI, 1.04–2.64) and for CHD mortality (RR, 2.35; 95% CI, 1.03–5.35) compared with control subjects. Analysis of event rates for a primary event by the FDA on the LIFE database shows that the event rates for the primary end-point increased as the BP control category worsened—worse control was associated with poorer outcomes (20). Thus, goal BP is more important than initial therapy. However, the choice of agent makes a significant difference in outcomes. It is possible that in ALLHAT, a poor regimen (lisinopril-based) that led to greater discontinuations and higher BP caused the increased morbidity and mortality. Thus, the choice of regimen, not just the initial antihypertensive agent, makes a significant difference in outcomes.

Conclusions

From a public health standpoint, no reduction in BP is too small in reducing cardiovascular morbidity and mortality. Because there is proportional reduction in mortality with BP reduction at least until a usual BP of 115/75 mmHg, a paradigm is emerging to lower BP to the lowest possible level that is best tolerated by the patient. There is no J-curve demonstrable that increases cardiovascular risk with lower BPs. Diuretics have reemerged as important agents to control hypertension and to reduce cardiovascular morbidity and mortality. Most patients will need 2 or more drugs to control hypertension, and a diuretic should be a part of any multidrug regimen. ACE inhibitors have an important place in the management of hypertension (Fig 1). In the high-risk population, they can reduce cardiovascular morbidity and mortality. Angiotensin II receptor blockers provide similar cardiovascular protection in hypertensive patients with LVH. Secondary analyses of clinical trials suggest that both ACE inhibitors and angiotensin II receptor blockers protect from new-onset diabetes mellitus. Furthermore, the combination of low-dose thiazide diuretics with ACE inhibitors or angiotensin II receptor blockers mitigates the metabolic side effects of either agent. Thus, they are excellent agents for synergistic reduction in BP. Physicians should not hesitate to use combination therapy to improve patient compliance and encourage participation of the patient through simple programs such as home BP monitoring (21). Dihydropyridine calcium-channel

blockers should be third-line agents unless there are compelling indications; the increased incidence of heart failure when compared with diuretics despite similar BP control in the 2 groups was seen in ALLHAT and supports other meta-analyses. Furthermore, no additional organ protection was seen in the amlodipine group compared with the chlorthalidone group. In black patients, beta-blockers appear to provide more protection than angiotensin receptor blockers in the hypertensive population with LVH. In black patients with hypertensive renal disease, ACE inhibitors appear to be superior to beta-blockers. The choice of the initial agent, the crafting of an appropriate regimen, and above all, the achievement of goal BP are important to reduce the cardiovascular burden of disease in the population.

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