Pulse Pressure Changes With Six Classes of Antihypertensive Agents in a Randomized, Controlled Trial

William C. Cushman, Barry J. Materson, David W. Williams, Domenic J. Reda, for the Veterans Affairs Cooperative Study Group on Antihypertensive Agents

Abstract—Pulse pressure has been more strongly associated with cardiovascular outcomes, especially myocardial infarction and heart failure, than has systolic, diastolic, or mean arterial pressure in a variety of populations. Little is known, however, of the comparative effects of various classes of antihypertensive agents on pulse pressure. In retrospective analyses of the Veterans Affairs Single-Drug Therapy for Hypertension Study, we compared changes in pulse pressure with 6 classes of antihypertensive agents: 1292 men with diastolic blood pressure of 95 to 109 mm Hg on placebo were randomized to receive hydrochlorothiazide, atenolol, captopril, clonidine, diltiazem, prazosin, or placebo. Drug doses were titrated to achieve a goal diastolic blood pressure of <90 mm Hg during a 4- to 8-week medication titration phase. Pulse pressure change (placebo subtracted) was assessed from baseline to the end of the 3-month titration and 1-year maintenance. Mean baseline systolic, diastolic, and pulse pressures were 152, 99, and 53 mm Hg, respectively. Reductions in pulse pressure during titration were greater (P<0.001) with clonidine (6.7 mm Hg) and hydrochlorothiazide (6.2 mm Hg) than with captopril (2.5 mm Hg), diltiazem (1.6 mm Hg), and atenolol (1.4 mm Hg); reduction with prazosin (3.9 mm Hg) was similar to all but clonidine. After 1 year, pulse pressure was reduced significantly more (P<0.001) with hydrochlorothiazide (8.6 mm Hg) than with captopril and atenolol (4.1 mm Hg with both); clonidine (6.3 mm Hg), diltiazem (5.5 mm Hg), and prazosin (5.0 mm Hg) were intermediate. These data show that classes of antihypertensive agents differ in their ability to reduce pulse pressure. Whether these differences affect rates of cardiovascular events remains to be determined. (Hypertension. 2001;38:953-957.)

Key Words: pulse pressure • antihypertensive agents • drug therapy • human

Pulse pressure (PP) has usually been found to be a stronger independent predictor of cardiovascular events, particularly in older populations, than has systolic (SBP), diastolic (DBP), or mean arterial pressure. Although treatment of elevated DBP or isolated SBP with antihypertensive agents has been shown to reduce cardiovascular events in prospective randomized controlled trials, clinical trials have not evaluated whether any reduction in cardiovascular events has been related to a reduction in PP. In fact, most studies assessing the antihypertensive efficacy of lifestyle interventions or drugs have addressed reductions in DBP and, to a limited extent, SBP. Studies have demonstrated differences in DBP and SBP antihypertensive efficacy between drug classes overall and in various demographic groups. Only very recently have studies begun to evaluate changes in PP, and almost no data have been published on the comparative effects of different classes of antihypertensive agents on PP.

Therefore, we compared the short- and long-term effects on changes in PP of a diuretic (hydrochlorothiazide), a β-blocker (atenolol), a calcium channel blocker (diltiazem sustained release [SR]), an ACE inhibitor (captopril), an α1-blocker (prazosin), and a central α2-agonist (clonidine) in a retrospective analysis of the Department of Veterans Affairs (VA) Single-Drug Therapy for Hypertension Study. The methods for this VA cooperative study were described in more detail previously. In brief, 1292 men from 15 US VA Medical Centers with DBP of 95 to 109 mm Hg on 2 consecutive visits while taking only single-masked placebo were randomly assigned to receive hydrochlorothiazide (12.5 to 50 mg once daily), atenolol (25 to 100 mg once daily), diltiazem SR (60 to 180 mg twice daily), captopril (12.5 to 50 mg twice daily), prazosin (2 to 10 mg twice daily), clonidine (0.1 to 0.3 mg twice daily), or placebo. All medications could be titrated over 3 dose levels as tolerated and needed to achieve a goal DBP of <90 mm Hg. If DBP was controlled and the medication was tolerated, the patient entered a 1-to-2-year maintenance phase. The primary outcome of the trial was “success” in maintaining the patient on medication and maintaining DBP <95 mm Hg for 1 year. If DBP was not controlled, participants were randomized to one of the alternative active agents after another placebo washout period. If DBP was still not controlled with the alternative monotherapy, the first agent was added to the second agent to assess control with the combination.
Demographics, medical history, and physical examination—including BP, heart rate, height, and weight—were obtained before randomization on placebo. BP, heart rate, and weight were also obtained periodically throughout the trial. A visit BP was the mean of 3 measurements (SBP and DBP were first and fifth phases of Korotkoff sounds, respectively) obtained with a standard mercury sphygmomanometer with the patient seated in a chair with back support. This report is a post hoc retrospective analysis of data from this randomized VA cooperative study, which was conducted from November 1986 to September 1990. Patients were recruited and followed up in 15 clinical sites: Dallas, Tex; Houston Tex; Jackson, Miss; Memphis, Tenn; Saint Louis, Mo; Washington, DC; Allen Park, Mich; Boston, Mass; East Orange, NJ; Manhattan, NY; Miami, Fla; Milwaukee, Wis; San Francisco, Calif; San Juan, Puerto Rico; and Topeka, Kan. Age and race subgroups were defined as black (African American), white, younger (<60 years of age), and older (>60 years of age). The age groupings were prespecified for subgroup analyses. In addition, in patients >60 years of age, SBP and PP became more strongly related to risk for cardiovascular events in the Framingham Heart Study.18 PP was calculated by subtracting DBP from SBP. Mean arterial pressure was calculated as 2/3 DBP+1/3 SBP. We retrospectively defined a PP goal of <50 mm Hg to make comparisons between drugs and combinations, because this is the PP goal recently recommended for consideration in therapeutic studies by the European Society of Hypertension.59

Statistical Analysis

ANOVA was used as the primary statistical comparison between mean changes in BP variables to evaluate whether any differences existed among the treatment groups. When the results were significant at P≤0.05, Tukey’s procedure for multiple comparisons was used to determine which pairs were different.29 We used χ² tests for comparison of categorical variables. Multiple linear regression analysis for each treatment group was used to evaluate the effect on PP change of age, race, location of residence (whether living in the southeast United States (“Stroke Belt”) or in another part of the United States), income, medication adherence, baseline DBP, body mass index (BMI), alcohol consumption, current cigarette smoking, heart rate, 24-hour urinary potassium and sodium excretion, plasma renin activity, serum potassium, creatinine, and glucose. The southeastern United States is considered the “Stroke Belt” because this region has had the highest rates for stroke mortality in the United States throughout much of the past century.

All analyses were done with SAS version 6.21 A value of P≤.05 was the criterion for statistical significance, and all statistical tests were 2 sided. For the regression analyses, P≤0.05 was the criterion for variable selection.

Results

Table 1 displays baseline characteristics for all 1292 study participants and by age-race subgroups. Previous reports have shown that the baseline characteristics were well balanced across the 7 treatment groups.14 Average age was 59 years, and average baseline BP was 152/99 mm Hg. PP was 53±13 mm Hg in all participants and averaged less in younger whites and blacks (49±12 and 47±12 mm Hg, respectively) than in older whites and blacks (56±12 and 57±12 mm Hg, respectively) (P<0.001).

During the titration phase, mean SBP was reduced significantly more with clonidine, hydrochlorothiazide, and diltiazem and reduced least with captopril (Table 2). DBP was reduced the most with diltiazem. Mean arterial pressure was

### Table 1. Baseline Characteristics for All Participants and by Age-Race Subgroup

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n=1292)</th>
<th>Younger Whites (n=246)</th>
<th>Younger Blacks (n=291)</th>
<th>Older Whites (n=408)</th>
<th>Older Blacks (n=330)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59±10</td>
<td>51±7</td>
<td>49±9</td>
<td>66±4</td>
<td>66±4</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>152±14</td>
<td>149±13</td>
<td>147±13</td>
<td>154±13</td>
<td>157±13</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>99±3</td>
<td>99±3</td>
<td>100±4</td>
<td>98±3</td>
<td>100±3</td>
</tr>
<tr>
<td>PP, mm Hg</td>
<td>53±13</td>
<td>49±12</td>
<td>47±12</td>
<td>56±12</td>
<td>57±12</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>74±11</td>
<td>75±11</td>
<td>76±11</td>
<td>73±11</td>
<td>74±11</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29±5</td>
<td>29±5</td>
<td>29±5</td>
<td>29±4</td>
<td>29±5</td>
</tr>
<tr>
<td>Drug treatment at screening, %</td>
<td>71</td>
<td>67</td>
<td>67</td>
<td>74</td>
<td>73</td>
</tr>
</tbody>
</table>

Values are mean±SD when appropriate. Younger age is <60 years; older age ≥60 years.

### Table 2. Changes in SBP, DBP, and Mean Arterial and Pulse Pressures by Drug During the 4- to 8-Week Titration Phase

<table>
<thead>
<tr>
<th></th>
<th>HCTZ</th>
<th>Atenolol</th>
<th>Captopril</th>
<th>Clonidine</th>
<th>Diltiazem</th>
<th>Prazosin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>−14±11 AB</td>
<td>−11±12 BC</td>
<td>−9±10 C</td>
<td>−16±13 A</td>
<td>−13±9 AB</td>
<td>−12±12 BC</td>
<td>−3±10 D</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>−10±6 B</td>
<td>−12±6 B</td>
<td>−9±7 C</td>
<td>−12±6 AB</td>
<td>−14±5 A</td>
<td>−11±7 BC</td>
<td>−5±7 D</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>−11.5±6.9 BC</td>
<td>−11.5±7.6 BC</td>
<td>−9.4±7.0 B</td>
<td>−13.6±7.6 CD</td>
<td>−13.8±5.3 D</td>
<td>−11.4±7.9 BC</td>
<td>−4.3±7.2 A</td>
</tr>
<tr>
<td>PP, mm Hg</td>
<td>−3.5±9.1 CD</td>
<td>1.3±9.6 AB</td>
<td>0.2±8.9 AB</td>
<td>−4.0±10.5 D</td>
<td>1.1±7.5 AB</td>
<td>−1.2±9.3 BC</td>
<td>2.7±8.5 A</td>
</tr>
<tr>
<td>Younger whites</td>
<td>−4.5±9.7 A</td>
<td>−1.2±8.4 AB</td>
<td>−0.3±6.5 AB</td>
<td>−3.6±10.2 AB</td>
<td>1.4±7.4 B</td>
<td>1.2±8.8 AB</td>
<td>−0.2±6.9 AB</td>
</tr>
<tr>
<td>Younger blacks</td>
<td>−4.0±7.4 B</td>
<td>3.8±6.9 A</td>
<td>1.1±8.7 AB</td>
<td>−3.9±7.0 B</td>
<td>0.2±8.8 AB</td>
<td>0.1±9.5 AB</td>
<td>3.1±8.9 A</td>
</tr>
<tr>
<td>Older whites</td>
<td>−2.2±9.9 BC</td>
<td>0.8±11.8 ABC</td>
<td>−0.1±8.5 ABC</td>
<td>−3.7±10.5 C</td>
<td>1.8±7.3 AB</td>
<td>−3.1±9.1 BC</td>
<td>3.8±8.7 A</td>
</tr>
<tr>
<td>Older blacks</td>
<td>−4.2±9.1 B</td>
<td>1.9±8.9 A</td>
<td>0.3±10.8 AB</td>
<td>−4.7±13.3 B</td>
<td>0.5±7.0 AB</td>
<td>−1.6±9.8 AB</td>
<td>2.2±8.3 A</td>
</tr>
</tbody>
</table>

HCTZ indicates hydrochlorothiazide; MAP, mean arterial pressure. Rows with letters indicate there are statistically significant differences (P<0.05) between drug groups; drug groups that share a letter in a row are not different from one another. For example, with regard to SBP, clonidine is significantly different from atenolol, captopril, prazosin, and placebo but not HCTZ or diltiazem. Also, HCTZ is significantly different from captopril and placebo, diltiazem is significantly different from captopril and placebo, and prazosin and captopril are different from placebo.
reduced the most with diltiazem and reduced the least (of active medications) with captopril. In all participants, PP was reduced significantly more with clonidine and hydrochlorothiazide than with captopril, diltiazem, atenolol, and placebo. Clonidine also reduced PP significantly more than did prazosin (Table 2). We defined an arbitrary PP goal of <50 mm Hg. Clonidine (57%) and hydrochlorothiazide (55%) achieved this goal the most often compared with 39% to 45% for the other active drugs and 38% for placebo (Figure 1); clonidine and hydrochlorothiazide were significantly different from diltiazem and placebo (P < 0.001). In the age-race subgroups, PP was reduced more with hydrochlorothiazide and clonidine than with atenolol and placebo in younger and older blacks, more with clonidine than with diltiazem and placebo in older whites, and more with hydrochlorothiazide than with diltiazem in younger whites (Table 2).

Because this was a diastolic entry and efficacy study, several factors, including regression to the mean, may have contributed to the 5-mm Hg reduction in DBP with placebo during the titration phase. To account for this placebo effect after randomization, we calculated the placebo-subtracted PP during the titration phase and after 1 year of therapy (Figure 2). During titration, mean placebo-subtracted PP was reduced more with clonidine (−6.7 mm Hg) than with all other active drugs except hydrochlorothiazide (−6.2 mm Hg), and hydrochlorothiazide reduced PP more than all but clonidine and prazosin. After 1 year, hydrochlorothiazide (−8.6 mm Hg) reduced placebo-subtracted PP significantly more than did captopril and atenolol (both −4.1 mm Hg).

When the PP goal of <50 mm Hg was assessed in patients receiving combinations of 2 drugs after the failure of each (randomly selected) to control DBP, combinations that included hydrochlorothiazide (74%) were significantly better (P = 0.003) than were combinations that did not include hydrochlorothiazide (43%) (Figure 3). No other comparison of combinations with or without each drug was significantly different.

In regression analyses (data not shown), increasing creatinine tended to increase the effect of hydrochlorothiazide on PP (P = 0.091); black race (P = 0.013), higher urinary potassium (P = 0.146), and current cigarette smoking (P = 0.016) decreased the effect of atenolol on PP; BMI increased the effect of captopril on PP (P = 0.109); higher plasma renin activity decreased the effect of clonidine on PP (P = 0.086); younger age (P = 0.139), improved medication adherence (P = 0.103), increasing heart rate (P = 0.105), increasing urinary sodium (P = 0.049), and drinking > 1 alcohol drink per day (P = 0.115) decreased the effect of diltiazem on PP; and black race (P = 0.095), medication adherence (P = 0.001), urinary sodium excretion (P = 0.045), and BMI (P = 0.047) decreased the effect of prazosin on PP. Living in the southeastern United States (P = 0.114) and increasing serum glucose (P = 0.086) increased the effect of prazosin on PP.

As reported previously, clonidine and prazosin were associated with the greatest frequency of symptomatic adverse effects and drug withdrawals during titration (14% and 12%, respectively, compared with 3% to 7% for the other drugs).

Discussion

In these analyses of the VA Single-Drug Therapy for Hypertension Study, we have shown that there are differences in the effects of 6 classes of antihypertensive agents on PP calculated by subtracting mean visit DBP from mean visit SBP. Although clonidine was very effective in reducing SBP, DBP, and PP during the titration phase, and SBP and PP quantitatively more than any other drug, it was associated with a much higher incidence of symptomatic adverse effects and drug withdrawals. The diuretic hydrochlorothiazide, which was well tolerated, also reduced PP as effectively as clonidine during titration and quantitatively the most, and it was statistically superior to the β-blocker and ACE inhibitor after 1 year of maintenance monotherapy. This greater reduction in

![Figure 1](image1.png)

**Figure 1.** Percentage of patients with PP <50 mm Hg on each drug during titration. HCTZ indicates hydrochlorothiazide; ATEN, atenolol; CAPT, captopril; DILT, diltiazem SR; CLON, clonidine; and PRAZ, prazosin. Arrows designate drugs that are not significantly different from each another; eg, CLON and HCTZ are significantly different from DILT and PLAC.

![Figure 2](image2.png)

**Figure 2.** Change in PP with each drug at end of titration and after 1 year (placebo subtracted). Statistically significant (P < 0.05) differences were as follows: during titration, CLON was significantly greater than all but HCTZ and HCTZ was significantly greater than CAPT and ATEN. Abbreviations as in Figure 1.

![Figure 3](image3.png)

**Figure 3.** Percentage of patients with PP <50 mm Hg in combinations of 2 drugs that included (with) or did not include (without) the listed drug after failure to control diastolic blood pressure with monotherapy with each of 2 randomly selected drugs. Only the comparison of combination with and without HCTZ was significantly different (P = 0.003). Abbreviations as in Figure 1.
PP with a diuretic compared with a β-blocker is similar to the experience in the Medical Research Council Mild Hypertension Trial. In each of the 4 age-race groups, clonidine and hydrochlorothiazide also reduced PP quantitatively more than the other drugs, except in older whites, in whom prazosin reduced PP quantitatively slightly more than hydrochlorothiazide, but not to a significantly different degree. When a PP goal of <50 mm Hg was used as an indication of PP control, clonidine and hydrochlorothiazide had the greatest PP control rates (55% to 57%). The calcium channel blocker diltiazem was no better than placebo in reaching this goal (39% versus 38%, respectively).

Most patients with hypertension will require >1 drug to reach the currently recommended SBP and DBP combined goals. Our results, showing that combinations that included the thiazide diuretic were superior to combinations without a diuretic in reducing PP, give strength to recommendations to include a diuretic in most multidrug antihypertensive regimens. This is also consistent with our previous report that the thiazide diuretic were superior to those without a diuretic for achieving SBP <140 mm Hg (77% versus 46%, respectively) or DBP <90 mm Hg (69% versus 51%).

As with clonidine, prazosin was associated with a significantly higher incidence of adverse effects and drug withdrawals. In addition, the α-blocker doxazosin was associated with significantly higher rates of cardiovascular events, especially heart failure, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), making α-blockers inappropriate for monotherapy of hypertension. It is of interest that in ALLHAT the diuretic and α-blocker reduced DBP to a similar extent, but SBP and therefore PP were reduced significantly more with the diuretic.

The mechanisms by which these classes of drugs differ in their effect on PP were not addressed in this study. However, we and others have shown comparatively large reductions in SBP and higher SBP control rates with diuretics but also with clonidine and calcium channel blockers. Although calcium blockers usually lower SBP as well as diuretics do, as in the current trial, DBP is usually lowered more consistently, resulting in less reduction in PP with calcium blockers than with diuretics. It is not clear whether the differences in PP found in this study are related to differences in vascular compliance.

In a variety of epidemiological studies, PP has been found to be a stronger predictor for future risk of cardiovascular events than SBP, DBP, or mean arterial pressure, particularly in older individuals. For example, in an older cohort of the Framingham Heart Study, a BP of 170/70 mm Hg was associated with approximately twice the risk of coronary heart disease events as a BP of 170/100 mm Hg. Although a reduction in DBP and/or SBP in clinical trials has resulted in reductions in cardiovascular events—particularly stroke, coronary events, and heart failure—in the Systolic Hypertension in the Elderly Program (SHEP) trial, participants in the actively treated group with the greatest reduction in DBP while SBP was being treated to goal had the least protection from cardiovascular events, perhaps reflecting an inability to decrease PP sufficiently in these participants. Our data cannot address whether a difference in reduction in PP between drug classes will result in a corresponding difference in the incidence of cardiovascular events or whether recommendations for selection of drug classes should be influenced by how well PP is reduced. Ongoing clinical trials, especially ALLHAT, will have the opportunity to evaluate the effect of differences in PP reduction on the incidence of cardiovascular events. Although the VA Single-Drug Therapy for Hypertension Study is a large, efficacy-comparison, randomized, controlled trial, it is also limited in that there were no women in the study population, it was conducted in men who met elevated diastolic entry criteria, and the current report is based on retrospective analysis.

In conclusion, we have shown that classes of antihypertensive agents differ in their ability to reduce PP. Hydrochlorothiazide and clonidine demonstrated the most consistent reductions in PP, but clonidine was associated with a much higher incidence of side effects and drug withdrawals, and central α-agonists have not been shown to reduce cardiovascular events as initial therapy in clinical trials. In addition, combination regimens that included hydrochlorothiazide were much more effective in reducing PP to <50 mm Hg. Whether differences in changes in PP by antihypertensive agents affect rates of cardiovascular events remains to be demonstrated.

References


Pulse Pressure Changes With Six Classes of Antihypertensive Agents in a Randomized, Controlled Trial
William C. Cushman, Barry J. Materson, David W. Williams, Domenic J. Reda and for the Veterans Affairs Cooperative Study Group on Antihypertensive Agents

Hypertension. 2001;38:953-957
doi: 10.1161/hy1001.096212

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/38/4/953

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/