SUMMARY We compared the effect on serum lipids of an α-blocker (prazosin) and a diuretic (hydrochlorothiazide) used as initial antihypertensive drug treatment for 102 men and women with less severe hypertension (average entry blood pressure, 148/97 mm Hg, with no major organ system damage). A two-center trial randomized patients to treatment with either prazosin or hydrochlorothiazide; the alternate drug was added if adequate blood pressure control was not achieved with the originally assigned drug, and patients were removed from any drug they were not able to tolerate. After an average of 40 weeks on the assigned drug regimen, a decline was observed in prazosin-treated patients in both serum total cholesterol (—9.3 mg/dl) and serum triglycerides (—33.9 mg/dl). In contrast, an increase in both these lipids was seen in hydrochlorothiazide-treated patients (+5.0 mg/dl for serum total cholesterol and +18.6 mg/dl for serum triglycerides). The net trial differences between the groups were 14.3 mg/dl for total cholesterol and 52.5 mg/dl for triglycerides, in favor of prazosin (p < 0.001 for both comparisons). These differences in lipids between the two groups persisted into the second year of the trial (p < 0.05). There were no significant differences between the drug groups in regard to the level of high density lipoprotein cholesterol or its subfractions or low density lipoprotein cholesterol. In patients who required a combination of the two drugs to achieve blood pressure control, the α-blocker diminished or eliminated the lipid-raising effects of the diuretic. Both drugs were similar in their ability to control the elevation of diastolic pressure. More patients were unable to tolerate prazosin than were unable to tolerate hydrochlorothiazide. For those able to continue with prazosin, either as the single initial treatment or in combination with hydrochlorothiazide, the lipid response appeared to be an asset in regard to avoiding possible atherogenic effects of treatment and thereby possibly reducing coronary risk. (Hypertension 12: 574-581, 1988)

KEY WORDS • antihypertensive agents • diuretics • adrenergic receptor blockade • prazosin • hydrochlorothiazide • clinical trial • serum lipids
vascular complications. BP eligibility was based on the mean diastolic level measured twice on each of two consecutive visits. The average of the two visits was required to be 90 to 130 mm Hg. Measurement was made on the right arm, with the patient seated, after a 5-minute rest for the first reading and a further rest between the first and second readings. The Hawksley Random Zero sphygmomanometer (Lancing, Sussex, UK) was used to measure BP.

Those excluded from the study were pregnant or lactating women, diabetics (taking medication or having glycosuria 2+ or fasting glucose ≥140 mg/dl on two measurements), persons with other metabolic disorders (e.g., thyroid disease) known to affect serum lipids, and persons taking drugs affecting either BP or lipids (e.g., other antihypertensive medication, oral contraceptives, or lipid-lowering drugs).

The planned duration of the study was 1 year for recruitment and at least 1 year of observation of patients receiving drug treatment.

Baseline and Randomization

Baseline evaluation included a comprehensive history and physical examination, electrocardiography, radiography, and fundoscopy. Fasting blood samples were drawn for a lipid profile and a comprehensive set of standard biochemical measurements using an automated instrument for multiple chemical analyses.

After baseline evaluation, those eligible persons who signed a consent form were randomly assigned to groups by a computer-generated code, with prior stratification by sex and initial diastolic BP (90-104 mm Hg and 105-130 mm Hg).

Treatment

Target BP was designated as less than or equal to 89 mm Hg or 10 mm Hg below entry mean diastolic BP, whichever was lower. (If BP was at goal level at the randomization visit, the patient was seen regularly but no drugs were prescribed unless the goal level was exceeded.)

Patients randomly assigned to the prazosin group were given an initial dose of a single 1-mg capsule to be taken before bedtime to avoid the possible first dose effect. Thereafter, 1 mg twice daily was prescribed. The dosage was then increased progressively at visits 2 weeks apart until target BP was achieved, or until a maximum dosage (10 mg twice daily) was reached, or limiting side effects occurred. The step-up schedule was 1 mg twice daily, 2 mg twice daily, 5 mg twice daily, and 10 mg twice daily.

For the group receiving hydrochlorothiazide, the initial dose was 25 mg/day. If target BP was not achieved in 4 weeks, this dosage was increased to 50 mg/day.

For patients in both groups whose diastolic BP was not at target level and was 85 mm Hg or higher after at least 4 weeks of treatment with the maximum dosage, BP was recorded, a blood sample was drawn to determine lipid levels with the assigned drug, and the alternate drug was added. The original drug was continued at maximum dose and the second drug was started, using the step-up schedule described above until the goal level was achieved. If diastolic BP did not reach the goal level with these two drugs, an appropriate third drug was used.

If the originally assigned drug was discontinued because of unacceptable side effects, the alternate drug was substituted after BP measurement and determination of lipid levels.

A modest effort, consistent with good medical practice, was made to help patients in both groups adopt a nutritional pattern to reduce excess intake of calories, sodium, and alcohol. Advice on these measures—as well as antismoking advice for cigarette smokers—was offered after drug treatment had been stabilized, but not earlier than 3 months after starting drug therapy.

Ongoing Evaluation

After baseline evaluation and adjustment of medication to reach targeted BP values, subsequent visits were scheduled every 3 months. At each of these visits, BP was recorded (two measurements in the sitting position and one in the standing position) using the Hawksley Random Zero sphygmomanometer. Body weight was also measured.

At baseline, at 3- and 6-month visits, and at 6-month intervals thereafter, a 12-hour fasting blood sample was drawn for lipid determinations. When the alternate agent to that originally assigned was added or substituted, blood samples were drawn prior to the change and at 3, 6, and 12 months after the change. In addition to lipid analyses, standard biochemical measurements were obtained at baseline and 6-month intervals. The serum potassium level was measured every 3 months. A review of symptoms, including patients' volunteered complaints, was recorded at each visit.

Lipid Analytical Methods

Serum total cholesterol and triglycerides were analyzed by automated enzymatic methods; the total high density lipoprotein cholesterol (HDL-C) level was measured after precipitation with heparin-manganese chloride. HDL-C Subclass 3 (HDL3-C) was measured after precipitation with dextran sulfate (molecular weight 15,000). HDL-C Subclass 2 (HDL2-C) was calculated by subtracting the value for HDL3-C from the total HDL-C. Very low density lipoprotein cholesterol (VLDL-C) was calculated by dividing serum triglycerides by five; low density lipoprotein cholesterol (LDL-C) was calculated by subtracting HDL-C and VLDL-C from total cholesterol.

Statistical Methods

The main statistical method was comparison of net mean changes between drug groups in lipids and BP, using the two-sample t test. When intradividual data were compared over time, paired t
Relative weight*  

TABLE 1. Comparability of Trial Groups at Baseline

<table>
<thead>
<tr>
<th>Baseline variable</th>
<th>Prazosin (n=49)</th>
<th>Hydrochlorothiazide (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>51.3±9.7</td>
<td>51.0±11.7</td>
</tr>
<tr>
<td>Male (%)</td>
<td>83.7</td>
<td>79.2</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>28.6</td>
<td>20.8</td>
</tr>
<tr>
<td>Black (%)</td>
<td>32.7</td>
<td>15.1</td>
</tr>
<tr>
<td>Serum total cholesterol (mg/dl)</td>
<td>229.6±42.3</td>
<td>229.4±39.4</td>
</tr>
<tr>
<td>Serum triglycerides (mg/dl)</td>
<td>173.9±79.6</td>
<td>166.6±120.8</td>
</tr>
<tr>
<td>Entry diastolic BP (mm Hg)</td>
<td>97.6±5.4</td>
<td>97.4±7.5</td>
</tr>
<tr>
<td>Entry systolic BP (mm Hg)</td>
<td>145.4±13.6</td>
<td>151.4±16.6</td>
</tr>
<tr>
<td>Resting pulse (beats/min)</td>
<td>74.5±8.2</td>
<td>74.8±12.8</td>
</tr>
<tr>
<td>Relative weight*</td>
<td>133.7±20.8</td>
<td>127.5±18.6</td>
</tr>
</tbody>
</table>

Values are means ± SD.  
*Ratio of observed to desirable weight for height and sex.  

Tests were used. Both internal and external (blind-replicate) quality control procedures were used to monitor the analytical laboratory procedures.

**Results**

Enrollment in the study totaled 102 hypertensive men and women. Recruitment began in May of 1984 and continued for more than 1 year; observation ended in May of 1986. By computer selection, 49 persons were randomly assigned at entry to the prazosin-treated group and 53 to the hydrochlorothiazide group. Table 1 presents baseline data on several characteristics (age, sex, race, smoking status, entry levels of BP and serum lipids, entry relative weight). As can be seen, the groups were similar in most aspects. The hydrochlorothiazide-treated group had somewhat higher mean systolic BP than the prazosin group, while the latter had a higher percentage of smokers. The percentage of black patients was higher in the prazosin than in the diuretic group.

Data on the effect of the drugs on lipids are available for 90 of the original 102 persons enrolled. Of the remaining 12 individuals without reportable data, 7 were early dropouts (less than 1 month after group assignment), 2 refused drugs after enrollment, 1 experienced an early rapid rise in BP requiring the alternate drug because of complaints 2 days after starting treatment, and 1 failed to have blood drawn prior to the addition of the alternate drug.

The data reported here on lipids and BP are for 90 patients while on the original assigned drug only, and for 21 of these patients while on both medications to achieve BP control. Side effects are reported for any time patients were on either or both of the drugs.

The lengthy recruitment period meant that approximately one half of those who began the trial completed 1 year or longer, with one half completing less than 1 year. The average time on the assigned drug was 40 weeks. Results are presented for specific lengths of time on the assigned drug and as trial averages for the entire time on the assigned drug.

Before completion of the study there were 5 dropouts from the prazosin group and 8 from the hydrochlorothiazide group. Their results were included for the period in which they were in the trial, and in the trial average for their assigned drug groups.

**Effects on Lipids**

**Serum Total Cholesterol**

Patients treated with hydrochlorothiazide experienced a mean rise in serum cholesterol as measured at each periodic evaluation during the trial (Table 2). In contrast, prazosin-treated patients experienced a mean fall in serum cholesterol, so that the net difference over time averaged 14 to 16 mg/dl between the two groups. This difference was statistically significant at each evaluation point. Patients taking prazosin remained on the assigned drug for an average of 38 weeks (SD, 31) and those taking hydrochlorothiazide, for 41 weeks (SD, 32).

The long-term effect on serum cholesterol was examined for the small cohort of patients treated with the assigned drug for more than 1 year (Table 3). A net difference of 17 to 22 mg/dl in favor of prazosin was seen without attenuation at each of the measurement points.

**Serum Triglycerides**

The response of serum triglycerides to the two drugs followed the same trend as observed for cholesterol, with the difference between the two groups more marked (Table 4). While on the assigned drug, patients in the prazosin-treated group experienced an average decline of 33.9 mg/dl in serum triglycerides, compared to an average rise of 18.6 mg/dl in the hydrochlorothiazide-treated group, for a net difference of 52.5 mg/dl (p < 0.001). The net difference increased over time (data not shown).

Since weight and weight change may influence triglyceride and cholesterol levels, both weight variables were examined in relation to lipid response. While both groups were on average considerably overweight at baseline, weight change was similar and minimal in both groups, averaging approximately 1 lb, so that this factor did not account for differential lipid response. The prazosin group in the first 6 months gained an average 1.44 lb (SD, 3.04) and the diuretic group lost 1.01 lb (SD, 2.77). Thus the more favorable lipid status was observed in the prazosin group despite a slightly unfavorable weight change as compared with hydrochlorothiazide-treated patients.

**Effects of Combined Therapy**

As noted, when target BP was not achieved with the assigned drug, the alternate drug was added. There were 21 patients on such combined therapy for a sufficient time to assess the effect on lipids. Addi-
TABLE 2. Comparison of Serum Total Cholesterol in Patients Treated with Prazosin or Hydrochlorothiazide: Trial Average and Periodic Measurements

<table>
<thead>
<tr>
<th>Time period</th>
<th>Baseline (mg/dl)</th>
<th>Treatment (mg/dl)</th>
<th>Change (mg/dl)</th>
<th>Net change* (mg/dl)</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>P (n=42)</td>
<td>227.7±40.5</td>
<td>218.3±38.7</td>
<td>-9.3±18.8</td>
<td>+14.3</td>
<td>3.50†</td>
</tr>
<tr>
<td>H (n=48)</td>
<td>228.9±38.8</td>
<td>233.2±40.8</td>
<td>+5.0±20.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>P (n=27)</td>
<td>238.7±37.0</td>
<td>232.3±35.9</td>
<td>-6.4±20.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>H (n=32)</td>
<td>226.0±37.8</td>
<td>234.2±46.2</td>
<td>+8.2±23.8</td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>P (n=20)</td>
<td>226.5±33.7</td>
<td>229.0±35.3</td>
<td>-7.6±17.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>H (n=23)</td>
<td>229.7±40.5</td>
<td>237.1±47.5</td>
<td>+7.3±21.3</td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>P (n=13)</td>
<td>235.2±34.7</td>
<td>220.2±34.3</td>
<td>-13.0±13.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>H (n=16)</td>
<td>229.9±45.4</td>
<td>233.2±48.1</td>
<td>+3.3±20.7</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD. P = prazosin; H = hydrochlorothiazide. The number of patients (n) includes all those with values obtained in the designated time period while on the assigned drug.

*Net difference between changes in the two groups.

†p < 0.001, †p < 0.01, §p < 0.05.

The addition of prazosin to hydrochlorothiazide overcame the cholesterol-raising effect of the diuretic (Table 5). While taking hydrochlorothiazide alone, these patients had experienced a rise from baseline of 9.7 mg/dl, but on combined therapy serum cholesterol fell 14.4 mg/dl as compared with single-drug treatment, with a net fall of 4.7 mg/dl as compared with baseline. Patients who had started with prazosin experienced a rise in cholesterol when the diuretic was added, but the combined effect was also an overall fall of 4.1 mg/dl as compared with baseline.

In regard to triglycerides, the addition of prazosin lessened but did not eliminate the lipid-raising effect of hydrochlorothiazide in patients originally treated with the diuretic alone (see Table 5). The addition of hydrochlorothiazide to prazosin treatment increased serum triglycerides, but the prazosin effect remained dominant, with an overall fall of 38.5 mg/dl as compared with baseline. It should be noted that patients originally treated with the diuretic generally had a longer period at the maximum diuretic dose (50 mg/day) before prazosin was added than did patients who were treated with prazosin before the diuretic was added. This may account for the continued difference observed in triglycerides of participants on combined therapy.

Fractions of Serum Total Cholesterol

Ongoing assessment of day-to-day laboratory technical error (see next section) was made possible by using split samples, with the laboratory blinded as to identification. However, the extended recruitment period made an evaluation of possible laboratory drift difficult. Baseline determinations were made over a year's time, so that data permitting such assessment accumulated slowly. Analyses of
TABLE 4. Comparison of Trial Average Levels of Serum Triglycerides in Patients Treated with Prazosin or Hydrochlorothiazide

<table>
<thead>
<tr>
<th>Drug</th>
<th>Baseline (mg/dl)</th>
<th>Treatment (mg/dl)</th>
<th>Change (mg/dl)</th>
<th>Net change (mg/dl)</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>P (n=42)</td>
<td>168.1±77.2</td>
<td>134.2±72.0</td>
<td>-33.9±49.2</td>
<td>+52.5</td>
<td>5.51*</td>
</tr>
<tr>
<td>H (n=48)</td>
<td>159.4±90.2</td>
<td>178.0±87.0</td>
<td>+18.6±39.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD. P = prazosin; H = hydrochlorothiazide.

*P < 0.001.

Laboratory Technical Error

Split samples were submitted to the laboratory for approximately 10% of all specimens, with different names and case numbers to mask true identification. Technical error, reflecting short-term variability in measurement, was 4.6 mg/dl for serum total cholesterol, 12.8 mg/dl for triglycerides, 4.1 mg/dl for HDL-C, and 4.6 mg/dl for HDL3-C. These represented 2.0%, 7.5%, 8.4%, and 12.7% of the means for total cholesterol, triglycerides, HDL-C, and HDL3-C, respectively.

Blood Pressure Control

Diastolic and systolic pressures were reduced significantly (p < 0.001) by both prazosin and hydrochlorothiazide. Both drugs reduced mean diastolic pressure from 97 mm Hg at baseline to a high normal trial average of 87 mm Hg for the period in which patients were taking the single drug to which they had been assigned (Table 7). Systolic pressure was reduced more in the hydrochlorothiazide-treated group than in the prazosin-treated group (p < 0.01) even though the hydrochlorothiazide group entered with a higher mean level than the prazosin group.

For those assigned to prazosin, the mean dose at the final visit was 8.8 mg/day; three quarters were taking 10 mg or less daily. One quarter of those assigned to hydrochlorothiazide were taking 25 mg/day at the final visit, while three quarters were taking 50 mg/day.

More patients originally treated with hydrochlorothiazide than with prazosin required addition of the alternate drug to achieve target diastolic pressure (23 for hydrochlorothiazide to 9 for prazosin). This partially reflects the shorter time allotted for hydrochlorothiazide therapy, as different names and case numbers were assigned to mask true identification. Technical error, reflecting short-term variability in measurement, was 4.6 mg/dl for serum total cholesterol, 12.8 mg/dl for triglycerides, 4.1 mg/dl for HDL-C, and 4.6 mg/dl for HDL3-C. These represented 2.0%, 7.5%, 8.4%, and 12.7% of the means for total cholesterol, triglycerides, HDL-C, and HDL3-C, respectively.

TABLE 5. Effect of Prazosin plus Hydrochlorothiazide on Serum Cholesterol and Triglyceride Levels: Trial Averages for Single vs Combined Drug Treatment

<table>
<thead>
<tr>
<th>Lipid measurement and initial drug</th>
<th>Baseline (mg/dl)</th>
<th>Single drug</th>
<th>Change</th>
<th>Combined drugs*</th>
<th>Change from single</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cholesterol (mg/dl)</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>P (n=8)</td>
<td>219.1±30.0</td>
<td>206.3±25.5</td>
<td>-12.8±13.7</td>
<td>215.0±31.9</td>
<td>+8.8±8.1</td>
<td>-4.1±12.4</td>
</tr>
<tr>
<td>H (n=13)</td>
<td>223.1±42.2</td>
<td>232.8±35.4</td>
<td>+9.7±18.6</td>
<td>218.4±33.5</td>
<td>-14.4±19.1</td>
<td>-4.7±20.8</td>
</tr>
<tr>
<td>Either (n=21)</td>
<td>221.6</td>
<td>—</td>
<td></td>
<td>217.1</td>
<td>—</td>
<td>-4.5</td>
</tr>
<tr>
<td><strong>Triglycerides (mg/dl)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P (n=8)</td>
<td>192.8±78.8</td>
<td>134.4±76.7</td>
<td>-58.4±44.7</td>
<td>154.3±85.0</td>
<td>+19.9±32.1</td>
<td>-38.5±44.5</td>
</tr>
<tr>
<td>H (n=13)</td>
<td>137.9±65.1</td>
<td>183.6±73.2</td>
<td>+43.9±43.2</td>
<td>177.3±75.0</td>
<td>-6.3±60.7</td>
<td>+37.6±66.1</td>
</tr>
<tr>
<td>Either (n=21)</td>
<td>159.9</td>
<td>—</td>
<td></td>
<td>168.5</td>
<td>—</td>
<td>+8.6</td>
</tr>
</tbody>
</table>

Values are means ± SD. P = prazosin; H = hydrochlorothiazide. P patients averaged 101.1 days on single drug and 200.9 days on combined drug treatment; H patients averaged 115.0 days on single drug and 326.0 days on combined drug treatment. *P was added to H or H to P if BP was not controlled on single drug.
TABLE 6. Comparison of Fractions of Serum Cholesterol in 42 Prazosin-Treated and 48 Hydrochlorothiazide-Treated Patients

<table>
<thead>
<tr>
<th>Cholesterol</th>
<th>Trial average (mg/dl)</th>
<th>Net change from baseline* (mg/dl)</th>
<th>t (for net change)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>52.1±9.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>53.8±15.3</td>
<td>+1.3</td>
<td>0.74</td>
</tr>
<tr>
<td>HDLrC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>34.8±5.6</td>
<td>+1.8</td>
<td>1.09</td>
</tr>
<tr>
<td>H</td>
<td>36.7±7.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDLrC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>17.4±6.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>17.3±10.0</td>
<td>-0.5</td>
<td>0.26</td>
</tr>
<tr>
<td>VLDL-C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>26.8±14.4</td>
<td>+10.5</td>
<td>5.53†</td>
</tr>
<tr>
<td>H</td>
<td>35.6±17.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>139.4±33.6</td>
<td>+2.5</td>
<td>0.63</td>
</tr>
<tr>
<td>H</td>
<td>144.3±42.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Trial average values are means ± SD. P = prazosin; H = hydrochlorothiazide. HDL-C = high density lipoprotein cholesterol; HDLrC = HDL-C Subclass 3; HDLrC = HDL-C Subclass 2; VLDL-C = very low density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol.

*Change is trial average minus baseline value. Net change is difference in amount of change between the two drug treatment groups (H minus P).

†p < 0.001.

Table 7 shows the trial average blood pressure response to prazosin or hydrochlorothiazide.

Discussion

The major findings of this randomized controlled trial of initial drug treatment of patients with less severe hypertension relate to the contrasting effects on serum lipids of the two drug regimens studied. The prazosin-treated group on average experienced a moderate fall in serum total cholesterol (−9.3 mg/dl) and a marked fall (20%) in serum triglycerides (−33.9 mg/dl). In contrast, there was a small average rise in serum total cholesterol (+5.0 mg/dl) and a 12% increase (+18.6 mg/dl) in serum triglycerides in the hydrochlorothiazide group. Both between-group differences are statistically significant. The findings are consistent with available data from other investigations, which were generally of shorter duration, with fewer patients, and often studied one or the other drug but not the two together.8, 13–21 In the present study, 90 patients, randomly assigned either to the α-blocker prazosin or the diuretic hydrochlorothiazide, completed an average of 40 weeks on the assigned drug regimens. A smaller subset of patients completed an average of 80 weeks, and therefore it was possible to examine among those in whom prazosin was discontinued were headache, nausea, and other gastrointestinal distress, and drowsiness. One case each of diaphoresis and priapism occurred. Among patients removed from hydrochlorothiazide, fatigue was the most common complaint; impotence, dizziness, and gouty arthritis were among other complaints reported as being of a marked degree. Similar complaints were made by the eight patients removed from combined prazosin and hydrochlorothiazide treatment. Most of these complaints were attributed to prazosin. Thus, the smaller proportion of prazosin than hydrochlorothiazide patients whose drug assignment had to be changed to obtain BP control (i.e., by added drugs) was balanced by the larger proportion of prazosin patients who had to be removed from their assigned drug regimen because of side effects. Overall, 17 of 42 prazosin patients (40%) and 22 of 48 hydrochlorothiazide patients (46%) were successfully treated with their single assigned drug (i.e., target BP was achieved and the drug was acceptable to the patient). The mean dose at the final visit for those 17 prazosin patients was 6 mg/day of prazosin; 9 of those 22 hydrochlorothiazide patients achieved goal pressure at a daily dose of 25 mg, while 14 were at 50 mg/day.
whether the contrasting effects of the two drugs on
lipids were transient or persistent. This is an im-
portant consideration given that the data from some (but
not all) studies indicate that the long-term lipid-
raising effects of orally administered diuretics are
sustained.9 22 23 For the time under observation,
there was a significant difference, in favor of prazo-
sin, in the effect on lipids for the first 6 months of the
study; the second 6 months, and the final period,
which averaged 6 additional months (i.e., the net
difference in effects on lipids persisted long term).

Since the protocol provided use of the alternate
drug if additional medication was needed for BP
control, it was possible to see if combined prazo-
sin-hydrochlorothiazide therapy could overcome or at
least diminish the lipid-raising effect of hydrochloro-
thiazide alone. This was in fact observed for both
serum total cholesterol and triglyceride levels. Such
combined therapy is not the only means to combat the
undesirable lipid-raising effects of diuretics. The find-
ings of the Multiple Risk Factor Intervention Trial,22
of Grimm et al.,9 and of our group in other studies,24
illustrate the positive effects, for example, of calorie
control and fat-modified diet composition on total
serum cholesterol, its fractions, and triglycerides.
Nonetheless, the findings here indicate that prazo-
sin can provide an additional, useful therapeutic path.

No significant differences were found between
the prazosin-treated and hydrochlorothiazide-
treated groups in HDL-C or its subfractions, HDL_{2}-
C and HDL_{3}-C. Both drug treatment groups were
similar in trial average levels of these variables, and
net differences from baseline were small and non-
significant. While the literature is not consistent
regarding the effect of either drug on HDL-C and its
subfractions, the general finding is a slight decrease
in HDL-C with diuretic treatment.8 9 25 26

In the present study, much—but not all—of the
net difference in serum total cholesterol between
the two groups was accounted for by the fall in VLDL-C in the prazosin group and the rise in
VLDL-C in the hydrochlorothiazide group, with a
significant net difference for this lipid fraction.
Although some other investigators have found a
decrease in LDL-C in prazosin-treated patients and
an increase in those treated with diuretics,9 19 21 in
the present study there was no significant between-
group difference in LDL-C.

In regard to BP control, both drugs were found
similar in their ability to maintain normal diastolic
pressure; systolic BP appeared to be better con-
trolled by the diuretic. This merits additional eval-
uation, in view of increasing evidence of the inde-
pendent contribution of elevated systolic pressure
to morbidity and mortality.27 Fewer patients ini-
tially treated with prazosin needed to have the
alternate drug added for better BP control, but this
was balanced by a larger proportion of prazosin-
treated patients who were removed from the drug
because of complaints. The number of patient com-
plaints attributed to prazosin was, in fact, consid-
erably higher than in previously published reports.28

In considering appropriate first-step drug therapy,
the ability to control BP to lower the risk of cardio-
vascular complications is, of course, of primary
concern. At the same time, the effect of antihyper-
tensive drugs on serum lipids is also an important
consideration. It has been estimated that a 1%
increase in total cholesterol is associated with a 2%
increase in risk of subsequent coronary mortality.29 31
The benefit of decreasing cardiovascular risk through
reduction of BP could be offset by an increase in risk
from a rise in lipid levels. In this regard, prazosin's
favorable effects on lipids should be considered in
the selection of initial antihypertensive drug therapy.
There remains the need for larger and longer trials to
test the ability of antihypertensive drugs to reduce
cardiovascular risk.32

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Kiang Liu.

<table>
<thead>
<tr>
<th>TABLE 8. Side Effects Reported by Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>P</strong></td>
</tr>
<tr>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Removed from drug</td>
</tr>
<tr>
<td>Reported effects of marked degree</td>
</tr>
<tr>
<td>Reported effects of moderate degree</td>
</tr>
<tr>
<td>Dosage before removal from drug</td>
</tr>
<tr>
<td>Prazosin</td>
</tr>
<tr>
<td>≤4 mg/day</td>
</tr>
<tr>
<td>5-9 mg/day</td>
</tr>
<tr>
<td>10 mg/day</td>
</tr>
<tr>
<td>14 mg/day</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
</tr>
<tr>
<td>25 mg/day</td>
</tr>
<tr>
<td>50 mg/day</td>
</tr>
<tr>
<td>Time on drug before removal</td>
</tr>
<tr>
<td>≤2 months</td>
</tr>
<tr>
<td>3-6 months</td>
</tr>
<tr>
<td>7+ months</td>
</tr>
<tr>
<td>Total no. of complaints of marked degree</td>
</tr>
<tr>
<td>30</td>
</tr>
</tbody>
</table>

Values are numbers of patients assigned to prazosin (**P**), hydrochlorothiazide (**H**), or combined treatment (**P + H**).

Type of complaints of marked degree (no. of patients in parentheses)

- **P**-treated: headache (4); nausea and/or diarrhea, cramps, vom-
it (7); drowsiness (3); postural hypotension (2); insomnia (2); impotence (2); lethargy, energy loss (2); pruritus, diaphoresis, nervousness, depression, nasal congestion, syncope, palpita-
tions, dry mouth, blurred vision, swellings, rash (1 each).

- **H**-treated: lethargy, fatigue (3); impotence, dizziness, consti-
pation, faintness, numbness and tingling, rash, flushing (1 each).

- **P + H**-treated: dizziness (2); impotence, dry mouth, consti-
pation, loss of energy, palpitations, nasal congestion (1 each).
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