A number of agents are now available to treat hypertension. One relatively new class of agents is the selective α₁-inhibitors, which have distinct advantages over earlier nonselective α-adrenergic receptor-blocking agents. Three α₁-inhibitors are reviewed in this article: prazosin, terazosin, and doxazosin. These α₁-inhibitors are similar in chemical structure and pharmacological action. α₁-Inhibitors lower blood pressure by reducing vascular tone in resistance and capacitance vessels. α₁-Inhibitors are similar in effectiveness in blood pressure lowering to other commonly used antihypertensive agents like the thiazide diuretic drugs and β-blockers, which are efficacious as monotherapy in lowering pressure, as initial agents, or in combination with other antihypertensive agents in multidrug therapeutic regimens. α₁-Inhibitors are associated with a reasonably low incidence of serious adverse effects and are essentially free of any adverse metabolic effects. α₁-Inhibitors have been shown to beneficially effect blood lipids in several studies. The favorable lipid effect makes α₁-inhibitors especially appropriate to use in diabetic hypertensive and other patients with elevated serum lipid levels. The beneficial lipid effects may enhance the ability of α₁-inhibitors to prevent coronary heart disease, an outcome that has been difficult to demonstrate in thiazide-based trials. (Hypertension 1989;13(suppl I):I-131—I-136)

A great deal of progress has been made during the past 30 years in developing drugs to treat hypertension. Today, the practitioner can select among several different classes of pharmacological agents, all of which are effective in lowering blood pressure and which have manageable side effects. Nonselective α-inhibitors like phenoxybenzamine and phentolamine were first used to treat hypertension in the mid-1950s. However, their usefulness was limited because of poor blood pressure-lowering efficacy and a high rate of unfavorable side effects, primarily marked tachycardia and a rapid development of loss of blood pressure efficacy.1 Therapeutic interest in α-inhibition has been renewed by the development of drugs that possess adrenoreceptor selectively. This new generation of α-inhibitors has many advantages over the original nonselective agents.

In 1976, the first selective α₁-inhibitor, prazosin, was introduced.2 Prazosin was highly preferable to previous α-inhibitors because it appeared to maintain local receptor-operator control mechanisms.3,4 Tachycardia and tolerance have not been problems with prazosin, an agent that has been used extensively for more than 10 years to treat hypertension. The selective α₁-inhibitors reviewed in this article are all quinazoline derivatives, which include prazosin, terazosin, and doxazosin. The chemical structures of these compounds are similar (Figure 1); terazosin differs from prazosin only in that the furan ring of the terazosin molecule is saturated. This structural difference accounts for terazosin’s longer half-life and allows this drug to be used once daily. The structure of doxazosin also allows for a longer duration of action and once-daily dosing. The pharmacology of the selective α₁-agents has recently been reviewed by Kyncl5 and Davey.6

Selective α₁-Inhibitors—Mechanism of Action

Selective α₁-inhibitors are all effective agents for lowering blood pressure by reducing peripheral vascular tone in resistance and capacitance vessels.7,8 This group of agents is highly selective for the postsynaptic α₁-receptors. This unique action probably allows the selective α₁-inhibitors to preserve feedback control on norepinephrine release, which may be responsible for preventing the undesired side effects of tachycardia and tolerance.3,4

Selective α₁-Inhibitors and Blood Pressure Control

The selective α₁-inhibitors, prazosin, terazosin, and doxazosin, have all been found to significantly
lower blood pressure in patients with uncomplicated hypertension. Prazosin has been demonstrated to be an effective antihypertensive agent in a number of studies.8,9 A recent report compared blood pressure lowering with terazosin to a placebo in a series of controlled trials (Table I).10 These trials were fixed-dose and titration studies with daily doses of terazosin ranging from 1 mg to 40 mg. Study participants were men and women ranging from 21 to 72 years old. Although these studies were not primarily designed to evaluate maximum blood pressure reduction, they showed that terazosin significantly lowered systolic and diastolic blood pressure by 8-12 mm Hg, an effect significantly different from placebo. Additional analyses from these studies showed the diastolic blood pressure response to the α1-inhibitor to be excellent. The response was very good or good (diastolic blood pressure <90 mm Hg at the final visit, a decrease of at least 10 mm Hg from baseline, or a decrease of 7–10 mm Hg from baseline but >90 mm Hg at the final visit) in 48% of those receiving terazosin compared with 33% taking placebo (p<0.05).11 Another study found that doxazosin and prazosin also lower blood pressure substantially compared with placebo, with observed changes in systolic and diastolic blood pressure for the α-blocker similar to those reported for terazosin.12

The hypotensive effect of selective α1-inhibitors has also been compared directly with that of the thiazide diuretic agents. Stamler et al.12 reported preliminary data on 62 hypertensive men and women in a randomized controlled trial comparing prazosin and hydrochlorothiazide. Participants were observed for a 3-month follow-up period. Both agents lowered diastolic blood pressure by a similar amount, averaging 10–11% for prazosin and 8–9% for hydrochlorothiazide. Doxazosin has also been compared with hydrochlorothiazide in double-blind controlled studies. In dosages of 1–16 mg doxazosin/day and 25–100 mg/hydrochlorothiazide/day, the two drugs showed similar results by significantly lowering standing and supine systolic and diastolic pressures. Both agents were clearly superior to placebo.14

The α-inhibitors prazosin and doxazosin have been compared with a number of β-adrenergic receptor-blocking agents. In several studies, systolic and diastolic blood pressure lowering is similar (8–12%) when selective α1-inhibitors are compared with various β-blockers.15,16

Blood pressure lowering with selective α1-inhibitors has also been studied by combining α-blockers with a variety of other classes of antihypertensive medications including diuretic agents and several β-blockers. These studies have found additional efficacy by adding α-inhibitors to these other agents.17,18

Metabolic Effects of α1-Inhibitors

One major advantage of α1-inhibitors is that they are essentially free of significant adverse metabolic effects. In controlled studies, the use of these agents has not been associated with significant adverse metabolic effects.11,20 In fact, several studies have observed that α1-inhibitors favorably benefit blood lipid levels.12,16,21–38 Table 2 summarizes lipid results from studies with the α1-inhibitors prazosin, terazosin, and doxazosin. Generally, this group of agents modestly lowers blood total cholesterol, low density lipoprotein cholesterol,
### Table 1. Blood Pressure Response to Terazosin in Five Placebo-Controlled Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of subjects</th>
<th>Mean baseline supine SBP</th>
<th>Mean baseline standing SBP</th>
<th>Mean change in supine SBP</th>
<th>Mean change in standing SBP</th>
<th>Percent change from baseline Supine</th>
<th>Percent change from baseline Standing</th>
</tr>
</thead>
<tbody>
<tr>
<td>M79-056</td>
<td>11</td>
<td>102.1±1.6</td>
<td>103.5±1.7</td>
<td>-10.1±4.3</td>
<td>-9.2±2.9</td>
<td>-6.6±5.3</td>
<td>-10.3±8.9</td>
</tr>
<tr>
<td>P-157.3±1.6</td>
<td>101.8±2.5</td>
<td>106.6±2.0</td>
<td>-1.1±5.0</td>
<td>-0.8±2.2</td>
<td>-1.1±5.6</td>
<td>-1.7±3.0</td>
<td></td>
</tr>
<tr>
<td>M80-033</td>
<td>17</td>
<td>100.1±1.6</td>
<td>100.4±0.9</td>
<td>-5.3±1.6</td>
<td>-5.1±0.9</td>
<td>-5.9±1.7</td>
<td>-6.4±1.0</td>
</tr>
<tr>
<td>P-150.4±1.6</td>
<td>101.0±1.6</td>
<td>104.7±1.1</td>
<td>-0.2±1.0</td>
<td>-1.4±1.1</td>
<td>+1.0±1.2</td>
<td>+1.0±1.3</td>
<td></td>
</tr>
<tr>
<td>M81-059</td>
<td>48</td>
<td>101.8±1.6</td>
<td>101.6±1.1</td>
<td>-5.5±2.0</td>
<td>-4.7±1.1</td>
<td>-6.7±2.0</td>
<td>-5.4±1.1</td>
</tr>
<tr>
<td>P-156.2±2.2</td>
<td>105.4±1.1</td>
<td>106.1±1.1</td>
<td>-4.4±2.3</td>
<td>-3.4±1.3</td>
<td>-0.6±2.3</td>
<td>-2.2±1.3</td>
<td></td>
</tr>
<tr>
<td>M81-060</td>
<td>54</td>
<td>100.2±1.6</td>
<td>103.3±1.0</td>
<td>-8.6±2.3</td>
<td>-8.8±0.9</td>
<td>-12.3±2.9</td>
<td>-9.0±1.3</td>
</tr>
<tr>
<td>P-147.0±2.2</td>
<td>100.4±1.2</td>
<td>103.2±1.2</td>
<td>-3.4±2.8</td>
<td>-5.5±1.1</td>
<td>-5.5±3.5</td>
<td>-5.1±1.6</td>
<td></td>
</tr>
<tr>
<td>M81-061</td>
<td>39</td>
<td>101.6±1.6</td>
<td>103.3±1.0</td>
<td>-8.6±2.3</td>
<td>-8.8±0.9</td>
<td>-12.3±2.9</td>
<td>-9.0±1.3</td>
</tr>
<tr>
<td>P-147.0±2.2</td>
<td>100.4±1.2</td>
<td>103.2±1.2</td>
<td>-3.4±2.8</td>
<td>-5.5±1.1</td>
<td>-5.5±3.5</td>
<td>-5.1±1.6</td>
<td></td>
</tr>
</tbody>
</table>

*All blood pressure values are in mm Hg.*

**Significant difference between treatment groups (p < 0.05).**

SBP, systolic blood pressure; DBP, diastolic blood pressure; T, terazosin; and P, placebo.


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**Grimm, 6-Antagonists in Hypertension Treatment**

**Adverse Effects of 6-Ahantagonists**

**Side Effects of 6-Ahantagonists**

Although no drug is totally free of side effects, 6-ahantagonists are a group as a rule of seriously adverse effects. The low incidence of serious side effects, overall, is similar to that of other commonly used classes of agents. In a large, well-controlled, multicenter study, the incidence of serious side effects was less than 0.5% in the 6-ahantagonist group, compared with approximately 1% in the placebo group. The most common side effects associated with 6-ahantagonists are dizziness and asthenia. Frank symptoms of side effects should be viewed with caution, as these effects may be exacerbated by concomitant use of other drugs. A small initial dose at bedtime, with this precaution, a first-dose response may be greatly reduced. This is similar to that reported for the 6-ahantagonists, sympathomimetics, and 6-ahantagonists. There is a theoretical difference in the incidence of side effects between classes of agents, and 6-ahantagonists are associated with a greater incidence of side effects.

**Percent change from baseline**

**Supine**

-6.6 -6.5†

**Standing**

-10.3 -8.9

1†-1.6

-0.7 -1.6

-7.5† -8.6†

-6.1 -8.9†

+0.6 +1.4 +1.6 +1.1

-3.4† -5.1†

-3.9† -6.4†

+0.1 +1.3 +0.7 -1.6

-3.5 -4.6 -4.3† -3.3†

+0.2 +0.4 +0.6 -2.1

-8.1 -8.9†

-8.3 -8.7†

-3.7 -5.5 -3.8 -5.1†

---

and triglycerides and increases high density lipoprotein cholesterol. Favorable changes in total serum lipids and lipoproteins are usually observed. This is in contrast to the treatment with thiazide diuretics, which may produce small increases in triglycerides and a decrease in HDL cholesterol. This apparent paradox has been explained by the fact that thiazides reduce total cholesterol by decreasing the synthesis of cholesterol and by increasing bile acid excretion. On the other hand, 6-ahantagonists appear to decrease total cholesterol by reducing the synthesis of cholesterol in the liver, and this effect is independent of the metabolic effects of the drugs. The decrease in triglycerides with 6-ahantagonists may be related to the inhibition of lipolysis in adipose tissue and to the increase in HDL cholesterol. However, the decrease in triglycerides may be due to the decrease in total cholesterol, and the increase in HDL cholesterol may be due to the decrease in total cholesterol. The overall effect of 6-ahantagonists on total serum lipids and lipoproteins is a decrease in total cholesterol and an increase in HDL cholesterol. This beneficial effect is similar to that of other agents that lower blood pressure, such as diuretics and 6-ahantagonists. However, the decrease in total cholesterol is not as pronounced with 6-ahantagonists as with diuretics, and the increase in HDL cholesterol is not as marked with 6-ahantagonists as with other agents. The beneficial effect of 6-ahantagonists on serum lipids and lipoproteins is consistent with the beneficial effect of these drugs on other cardiovascular risk factors. Thus, 6-ahantagonists appear to be an effective and safe class of antihypertensive agents, and they should be considered as an important tool in the management of hypertension.
TABLE 2. Effects of α1-Antagonists on Lipids and Lipoproteins: Within-Group Changes From Baseline by Study

<table>
<thead>
<tr>
<th>Agent and first author</th>
<th>Year</th>
<th>N</th>
<th>Duration of study (weeks)</th>
<th>Serum lipid measurements*</th>
<th>LDL cholesterol*</th>
<th>HDL cholesterol*</th>
<th>Triglycerides*</th>
<th>Cholesterol/ HDL cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prazosin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kirkendall et al²¹</td>
<td>1978</td>
<td>13</td>
<td>8</td>
<td></td>
<td>-5.3†</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Leren et al²²</td>
<td>1980</td>
<td>23</td>
<td>8</td>
<td></td>
<td>-9.0</td>
<td>...</td>
<td>-4.0‡</td>
<td>-16.5§</td>
</tr>
<tr>
<td>Leichter and Baumgardner²³</td>
<td>1981</td>
<td>7</td>
<td>...</td>
<td></td>
<td>-4.3</td>
<td>...</td>
<td>+6.0</td>
<td>+4.0</td>
</tr>
<tr>
<td>Velasco et al²⁴</td>
<td>1982</td>
<td>19</td>
<td>12</td>
<td>+7.5</td>
<td>...</td>
<td>+19.6†</td>
<td>...</td>
<td>-27.6†</td>
</tr>
<tr>
<td>Kokubu et al²⁵</td>
<td>1982</td>
<td>14</td>
<td>12</td>
<td>-0.7</td>
<td>...</td>
<td>+12.5†</td>
<td>...</td>
<td>0.9</td>
</tr>
<tr>
<td>Havard et al²⁶</td>
<td>1982</td>
<td>17</td>
<td>10</td>
<td>0</td>
<td>...</td>
<td>+10.5</td>
<td>...</td>
<td>-16.2</td>
</tr>
<tr>
<td>Lithell et al²⁷</td>
<td>1982</td>
<td>9</td>
<td>52</td>
<td>-3.2</td>
<td>-6.5</td>
<td>0</td>
<td>...</td>
<td>-0.7</td>
</tr>
<tr>
<td>Goto²⁸</td>
<td>1984</td>
<td>34</td>
<td>12</td>
<td>-1.1</td>
<td>+1.0</td>
<td>+4.0</td>
<td>...</td>
<td>-21.0</td>
</tr>
<tr>
<td>Lowenstein and Neusy²⁹</td>
<td>1984</td>
<td>29</td>
<td>8</td>
<td>-7.3</td>
<td>-9.4</td>
<td>+6.0</td>
<td>...</td>
<td>-20.0</td>
</tr>
<tr>
<td>Mauersberger³⁰</td>
<td>1984</td>
<td>15</td>
<td>8</td>
<td>-2.3</td>
<td>-15%</td>
<td>+10.8†</td>
<td>...</td>
<td>-3.2</td>
</tr>
<tr>
<td>Tskabatake et al³²</td>
<td>1984</td>
<td>15</td>
<td>52</td>
<td>+2.0</td>
<td>...</td>
<td>+17.0†</td>
<td>...</td>
<td>-7.3</td>
</tr>
<tr>
<td>Deger³³</td>
<td>1986</td>
<td>32</td>
<td>variable</td>
<td>-3.7</td>
<td>-5</td>
<td>+6.1</td>
<td>...</td>
<td>-12.5</td>
</tr>
<tr>
<td>Terazosin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deger³³</td>
<td>1986</td>
<td>128</td>
<td>variable</td>
<td>-2.5††</td>
<td>-2.7</td>
<td>+1.6</td>
<td>...</td>
<td>-6.8†</td>
</tr>
<tr>
<td>Degre³³</td>
<td>1986</td>
<td>38</td>
<td>8</td>
<td>-3.1</td>
<td>-5.6</td>
<td>+4.2</td>
<td>...</td>
<td>-9.5</td>
</tr>
<tr>
<td>Doxazosin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cox et al³⁴</td>
<td>1986</td>
<td>142</td>
<td>9-24</td>
<td>-1.2</td>
<td>...</td>
<td>+7.6</td>
<td>...</td>
<td>-9.0</td>
</tr>
<tr>
<td>Lehtonen et al³⁵</td>
<td>1986</td>
<td>21</td>
<td>20</td>
<td>-8.9††</td>
<td>-16.9††</td>
<td>+8.0†</td>
<td>...</td>
<td>-1.1</td>
</tr>
<tr>
<td>Torvik and Madsbu¹²</td>
<td>1986</td>
<td>46</td>
<td>12</td>
<td>-3.9</td>
<td>-5.5</td>
<td>+6.3</td>
<td>...</td>
<td>-12.6†</td>
</tr>
<tr>
<td>Frick et al³⁶</td>
<td>1986</td>
<td>39</td>
<td>20</td>
<td>-1.7</td>
<td>...</td>
<td>+3.9§</td>
<td>...</td>
<td>-5.0§</td>
</tr>
<tr>
<td>Pool³⁷</td>
<td>1987</td>
<td>43</td>
<td>10-24</td>
<td>+1.3</td>
<td>...</td>
<td>+0.8</td>
<td>...</td>
<td>-6.0†</td>
</tr>
<tr>
<td>Nash et al³⁶</td>
<td>1987</td>
<td>38</td>
<td>10</td>
<td>-2.9‡</td>
<td>...</td>
<td>+2.1†</td>
<td>...</td>
<td>-11.1‡</td>
</tr>
<tr>
<td>Trost et al³⁸</td>
<td>1987</td>
<td>19</td>
<td>24</td>
<td>-6.1††</td>
<td>-8.5</td>
<td>+13.0††</td>
<td>...</td>
<td>-17.4†</td>
</tr>
</tbody>
</table>

LDL, low density lipoprotein and HDL, high density lipoprotein.
*Values are in mg/dl.
†, Significant change from baseline; †*, significant change compared with placebo; ‡*, significant change compared with thiazide diuretic drug; §, significant change compared with β-blocker; and §*, significant change compared with other antihypertensive agent.
\( p > 0.05, \Delta p > 0.01, \$ p > 0.001.\)

In studies of terazosin and doxazosin. For all studies, approximately one half of those patients treated with α1-inhibitors report at least one adverse effect, which is usually mild to moderate in severity. Frequently, the placebo-treated patients have a similar number of complaints. It is noteworthy that impotence, a common side effect observed with many antihypertensive agents, occurs infrequently with α1-inhibitors and is usually not different compared with placebo.²⁰ Treatment with α1-inhibitors often results in some weight gain, usually 2–3 pounds, and peripheral edema is occasionally observed. Tachycardia and tolerance, which were common side effects with the earlier

TABLE 3. Prevalence of Side Effects in Studies of α1-Inhibitors: Within-Group Data

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Prazosin</th>
<th>Terazosin</th>
<th>Doxazosin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness or vertigo</td>
<td>5–31</td>
<td>14–22</td>
<td>10–38</td>
</tr>
<tr>
<td>Asthenia</td>
<td>10</td>
<td>8–14</td>
<td>1–7</td>
</tr>
<tr>
<td>Tiredness or fatigue</td>
<td>5</td>
<td>6</td>
<td>5–19</td>
</tr>
<tr>
<td>Syncope</td>
<td>&lt;1</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Impotence</td>
<td>10</td>
<td>5–14</td>
<td>4</td>
</tr>
<tr>
<td>Headache</td>
<td>5–40</td>
<td>4–13</td>
<td>4–11</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>5</td>
<td>6–10</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Impotence</td>
<td>5</td>
<td>2</td>
<td>1–3</td>
</tr>
</tbody>
</table>
nonselective α₁-inhibitors, are not notable problems with the newer selective α₁-inhibitors when used in the treatment of hypertension.

Discussion

A number of selective α₁-inhibitors have been studied to determine their usefulness as antihypertensive agents. Unlike the early nonselective α-blockers, the newer α₁-inhibitors are well tolerated and largely free of important adverse effects like tachycardia, diarrhea, and tolerance.

Selective α₁-inhibitors have been shown to be more effective than placebo in blood pressure lowering, with an efficacy similar to that of other commonly used antihypertensive agents like the thiazide diuretic drugs and β-blockers. When α₁-inhibitors are added to preexisting multiple-drug regimens, selective α-blockers have also been shown to provide additional efficacy in lowering blood pressure. α-Blockers are versatile and can be used alone as initial therapy or in combination with other agents in multiddrug regimens. Selective α₁-inhibitors as monotherapy will adequately control blood pressure in approximately one half the patients treated for "mild" diuretic hypertension (diastolic blood pressure 90–104 mm Hg). Selective α₁-inhibition lowers blood pressure by reducing the peripheral vascular tone in resistance and capacitance vessels.

Selective α₁-inhibitors are virtually free of adverse metabolic effects and offer at least theoretical advantages for treating hypertension in patients who also have diabetes, asthma, and peripheral vascular disease. Thus, these agents should be considered as initial antihypertensive agents for these patients. Because selective α₁-inhibitors are associated with slightly positive or neutral effects on blood lipoproteins, these drugs should also be considered, along with other lipid-neutral agents, as antihypertensive agents of choice for patients whose blood lipid levels require medical attention. New guidelines considerably broaden the number of patients who require treatment of their blood lipid levels.45

Like all drugs, selective α₁-inhibitors are associated with adverse effects. Approximately one half the patients taking α-blockers on a long-term basis will experience at least one side effect. These side effects are usually mild to moderate in severity. Dizziness, vertigo, asthenia, and fatigue are the most common side effects. The first-dose phenomenon, however, is rare (<1%) when α₁-inhibitors are given in small, carefully titrated, initial doses at bedtime.

Further investigation of selective α₁-inhibitors and other antihypertensive agents is needed to determine if the lack or presence of metabolic effects, like those on lipid and lipoprotein concentrations, is significant in preventing cardiovascular disease independent of the blood pressure–lowering effects, which are generally similar for most antihypertensive agents. The Treatment of Mild Hypertension Study is one that is currently addressing this important question in a long-term trial.46

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KEY WORDS • α-inhibitors • antihypertensive agents • α-blockers
alpha 1-antagonists in the treatment of hypertension.
R H Grimm, Jr

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