Effect of the HMG-CoA Reductase Inhibitors on Blood Pressure in Patients With Essential Hypertension and Primary Hypercholesterolemia

Nicola Glorioso, Chiara Troffa, Fabiana Filigheddu, Francesco Dettori, Aldo Soro, Paolo Pinna Parpaglia, Stefano Collatina, Marco Pahor

Abstract—Certain hydroxymethylglutaryl coenzyme A reductase inhibitors, ie, statins, may cause vasodilation by restoring the endothelial dysfunction that frequently accompanies hypertension and hypercholesterolemia. Several studies have found that a blood pressure reduction is associated with the use of statins, but conclusive evidence from controlled trials is lacking. After an 8-week placebo and diet run-in period, 30 persons with moderate hypercholesterolemia and untreated hypertension (total cholesterol 6.29±0.52 mmol/L, systolic and diastolic blood pressure 149±6 and 97±2 mm Hg) were randomized in a double-blind manner to placebo or pravastatin (20 to 40 mg/d) in a crossover design. In 25 participants who completed the 32-week trial, pravastatin decreased total and LDL cholesterol (both −1.09 mmol/L, P=0.001), systolic and diastolic blood pressure (−8 and −5 mm Hg, both P=0.001), and pulse pressure (−3 mm Hg, P=0.011) and blunted the blood pressure increase caused by the cold pressor test (−4 mm Hg, P=0.005) compared with placebo. It also reduced the level of circulating endothelin-1 (P=0.001). The blood pressure results were virtually unchanged in stratified analyses according to gender and age and in intention-to-treat analyses that included the 5 patients who dropped out of the study. When the participants were taking either placebo or pravastatin, blood pressure was not significantly correlated with total or LDL cholesterol or with circulating endothelin-1. Pravastatin decreases systolic, diastolic, and pulse pressures in persons with moderate hypercholesterolemia and hypertension. This antihypertensive effect may contribute to the documented health benefits of certain statins. (Hypertension. 1999;34:1281-1286.)

Key Words: statins ■ blood pressure ■ cholesterol ■ endothelin ■ hypertension, essential ■ hypercholesterolemia

Certain statins, or hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are clinically proven to prevent coronary and cerebrovascular events in persons with increased plasma cholesterol levels.1 In a large primary prevention trial,2 it has been observed that compared with placebo, pravastatin can decrease the risk of cardiovascular events early after randomization. These findings suggest that in addition to the long-term prevention of atherosclerosis, other more immediate mechanisms might account for the clinical benefits of statins.3

Several short-term studies have shown that statins can improve endothelial function and the endothelium-dependent arterial vasodilatation that are typically altered in persons with increased plasma cholesterol levels.4-7 Hypercholesterolemia, endothelial dysfunction, and hypertension are frequently coexisting conditions, even in the absence of documented atherosclerotic lesions.8-11 Moreover, recent animal data indicate that the effect of pravastatin on the endothelium might be due in part to nonlipid effects.12 In theory, by improving endothelial dysfunction, cholesterol reduction with statins may decrease blood pressure in persons with hypertension and hypercholesterolemia. In several animal and human studies, statins decreased resting or stress-induced blood pressure,13-18 but such an effect was not confirmed by other studies.19-24 Whether statins can decrease elevated blood pressure in hypertensive patients and whether this mechanism has clinical relevance for event reduction remain unanswered questions. The aim of the present study was specifically to assess in a randomized, double-blind crossover trial whether the HMG-CoA reductase inhibitor pravastatin decreased diastolic blood pressure by ≥5 mm Hg in persons with primary hypercholesterolemia and essential hypertension. Systolic and pulse pressures and the blood pressure response after cold pressor test were secondary outcomes.

Methods
The study was a randomized, double-blind, placebo-controlled crossover trial of pravastatin conducted at the Clinica Medica of the University of Sassari, Sardinia, Italy. The protocol was approved by the local ethics committee, and the participants gave written informed consent. The participants were men and women aged 40 to
70 years who had diastolic hypertension and primary hypercholesterolemia and who were not taking any lipid-lowering or antihypertensive drugs. To be eligible, the participants had to have a fasting total plasma cholesterol level >6.50 mmol/L, plasma triglycerides <2.66 mmol/L, diastolic blood pressure ≥90 mm Hg and ≤110 mm Hg, and systolic blood pressure <170 mm Hg. Blood pressure was measured with the subject in the sitting position between 8 and 10 AM in a quiet room by a trained nurse who was unaware of the cholesterol levels. Four consecutive measurements were taken over a 10-minute period with a mercury sphygmomanometer, and the average of the last 3 values was used. Exclusion criteria were a diagnosis of diabetes, liver disease, kidney disease, chronic pancreatitis, cancer, acute myocardial infarction, or unstable angina within 6 months; heart failure; type I, IIa, III, IV, or V dyslipidemia or any other severe condition with poor prognosis; smoking >10 cigarettes per day; drinking >36 g of alcohol per day; use of corticosteroids or hormone-replacement therapies; and being a premenopausal women not using an intrauterine contraceptive device.

A total of 49 participants meeting these criteria were enrolled in an 8-week run-in phase of the study to stabilize blood pressure and plasma cholesterol levels (weeks −8 to week 0). During this phase, the participants were given single-blind placebo between 9 and 10 PM each day and were assigned a daily diet containing 120 mmol of sodium and 2200 kcal, 30% of which came from fatty acids (10% saturated fatty acids). The patients were instructed to maintain the same diet throughout the study. Blood pressure, total cholesterol, body weight, compliance with study treatment as assessed by pill count (100 × number of pills taken/number of pills prescribed), and compliance with diet as assessed by interview and urinary sodium excretion were ascertained every 2 weeks. Routine blood examination tests and a physical examination were performed to exclude other comorbid conditions.

Participants were excluded if they had abnormal levels of plasma aldosterone, supine and standing plasma renin activity, 24-hour urinary catecholamines, or 24-hour urinary tetrahydrocortisol plus allotetrahydrocortisol/tetrahydrocortisone ratio, or if they had anomalies in the renal ultrasound scan or in renal arterial digital subtraction angiography, which was done if renal artery stenosis was suspected. Participants were also excluded if, at an average of 2 visits, they had urinary sodium excretion <80 or >200 mmol/24 hours, diastolic blood pressure <90 or >100 mm Hg, systolic blood pressure >170 mm Hg, total plasma cholesterol <5.98 or >7.80 mmol/L, weight change >2 kg, evidence of secondary hypertension, abnormal values in the routine laboratory tests, or compliance with treatment <90% or >110%.

The following exclusion criteria were met by 19 participants: low or high urinary sodium excretion (n = 1 and n = 3, respectively), high total plasma cholesterol (n = 5), body weight change (n = 2), high blood pressure (n = 3), abnormal blood tests (serum creatinine >133 μmol/L, n = 1; fasting glucose >7.7 mmol/L, n = 2), and withdrawal of consent (n = 2).

At the end of the run-in phase (week 0), which represents the baseline of the trial, 30 participants were randomized in a double-blind manner to 20 mg of pravastatin or placebo given between 9 and 10 PM every day for 16 weeks, followed by 16 weeks of crossover treatment. If total plasma cholesterol was >5.46 mmol/L 8 weeks after randomization or 8 weeks after crossover, the drug dose was doubled to 40 mg/d. Bristol Myers Squibb (Rome, Italy) provided the study drugs and allocated the treatments according to a computer-generated randomization sequence. The randomization codes were kept in individual sealed envelopes that could be opened in case of an emergency. Follow-up clinic visits were scheduled every 4 weeks to monitor blood pressure and biochemical measures. Fasting blood samples were drawn by venipuncture between 8 and 10 AM. Plasma total and HDL cholesterol and triglycerides, serum glucose, creatinine, sodium, potassium, uric acid, creatine phosphokinase, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, glycyltranferase, and 24-hour urinary sodium excretion were measured every 4 weeks.

At baseline and at the end of each 16-week period of randomized treatment, plasma renin activity, plasma aldosterone, and 24-hour urinary aldosterone excretion were measured by radioimmunoassay, and the cold pressor test was performed with the subject seated in a quiet room by measurement of systolic and diastolic blood pressure in the right arm with a mercury sphygmomanometer 15, 10, 5, and 0 minutes before and 30 seconds, 60 seconds, and 2, 5, and 10 minutes after immersion of the left arm in a bucket containing water and melting ice for 1 minute. Pulse pressure was calculated by subtraction of diastolic from systolic blood pressure. Mean blood pressure was calculated by the addition of two thirds of the pulse pressure to diastolic blood pressure. The Friedewald formula was used to calculate the LDL cholesterol level.28 Body mass index was calculated by dividing the weight in kilograms by the square of the height in meters.

Circulating endothelin-1 was measured by radioimmunoassay (Peninsula) after extraction of the plasma on C18 Sep-Pak cartridges. Plasma for endothelin-1 measurement was drawn in the morning at baseline (week 0), at crossover (week 16), and at the end of the study (week 32) and stored frozen until assayed.

Data Analysis

Results are presented as mean ± SD and 95% CI. Paired and unpaired Student’s t tests were used to compare differences between treatments as appropriate. Correlation analysis was used to study associations between blood pressure response and other variables. To assess potential carryover effects of treatment, the means at baseline (week 0) were compared with those at week 32 in the group randomized to the sequence pravastatin-placebo (points a and b in the Figure), and the means at week 16 were compared with those at week 32 in the group randomized to the sequence placebo-pravastatin (points c and d in the Figure). None of these comparisons reached statistical significance for any of the variables depicted in Tables 1 and 2 (P > 0.05), which suggests that after 16 weeks, there was no carryover effect of treatment. The results with pravastatin were therefore compared with those with placebo at the end of each 16-week period of randomized treatment. For the outcome of blood pressure, both intention-to-treat and per protocol analyses were performed. Intention-to-treat analyses include all the patients who did and did not drop out from treatment during the trial, whereas the per protocol analyses include only those patients who completed the trial.

By sample-size calculations, it was estimated that 30 participants needed to be randomized to detect a 5-mm Hg difference in diastolic blood pressure given a 10% dropout rate, power of 90%, α = 0.05, and a standard deviation for paired differences of 8. Because our estimate of the standard deviation for paired differences was conservative, a greater power was actually achieved in this study.

Results

A total of 30 participants (mean age 53 ± 2 years, range 40 to 68 years, 57% of whom were women) were randomized. During the run-in period of placebo and diet regimens, we observed a significant decrease compared with the initial values in systolic and diastolic blood pressures, total plasma cholesterol, and LDL cholesterol (Figure; P = 0.001 for all parameters), triglycerides (1.52 ± 0.45 to 1.36 ± 0.39 mmol/L; P = 0.026), urinary sodium excretion (137 ± 40 to 122 ± 51 mmol/24 hours; P = 0.007), and body mass index (25.8 ± 4.1 to 25.5 ± 4.0 kg/m²; P < 0.001). No significant changes in HDL cholesterol (1.43 ± 0.21 to 1.43 ± 0.29 mmol/L; P = 0.79) or other biochemical markers were found. Thereafter, the changes in blood pressure became marginal, although they were still present in those patients who were randomized to placebo compared with week 0.

During the double-blind randomization phase, 2 participants dropped out of the study while they were taking placebo...
Changes in systolic and diastolic blood pressures and total and LDL cholesterol levels according to treatment. ● indicates run-in placebo; ○, pravastatin followed by placebo; □, placebo followed by pravastatin; R, randomization; and C-O, crossover. To test potential carryover effects, blood pressure means were compared at points a vs b and c vs d (P>0.05 for all measures). $P=0.001$ for paired comparison at week 8 vs week 0 for all measures. $P=0.001$ for comparison of placebo vs pravastatin at week 16 for all measures.

because they had symptomatic hypertension (headache) and required a diuretic to treat hypertension; 1 patient taking pravastatin dropped out because of gastric pain and requirement of treatment for high blood pressure; and 1 patient dropped out while taking pravastatin and 1 while taking placebo because of poor compliance with diet, as determined by urinary sodium excretion. The remaining 25 participants completed the trial. Blood pressure measurements were obtained in all 30 randomized participants, whereas biochemical measures and cold pressor tests were available at all follow-up visits only for the 25 participants who completed the trial. In these 25 participants, the average total cholesterol level at baseline was 6.29±0.52 mmol/L, and as expected, pravastatin decreased the total cholesterol level by 17% compared with placebo (Table 1). Pravastatin also significantly decreased LDL cholesterol by 25% but had no significant effects on HDL cholesterol, triglycerides, plasma renin activity, urinary sodium excretion, other biochemical measures, or body mass index. Plasma and urinary aldosterone levels tended to be lower with pravastatin treatment than with placebo, but the difference did not reach statistical significance ($P=0.063$ and $P=0.083$, respectively).

The baseline systolic, diastolic, and pulse pressures were 149±6, 97±2, and 52±6 mm Hg, respectively (Table 2). After 16 weeks, compared with placebo, pravastatin significantly decreased systolic, diastolic, and pulse pressures by 8, 5, and 3 mm Hg, respectively ($P=0.001$, $P=0.001$, and $P=0.011$, respectively). Similar systolic and diastolic blood pressure reductions were achieved in the 7 participants who received 40 mg of pravastatin and the 18 participants who received 20 mg of pravastatin. After 16 weeks of pravastatin, systolic blood pressure decreased in all participants by 2 to 14 mm Hg compared with pretreatment placebo, except for 2

TABLE 1. Effect of Pravastatin on Biochemical Measures and Body Mass Index

<table>
<thead>
<tr>
<th>Measure</th>
<th>Randomized Treatments</th>
<th>$\Delta$ (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Placebo</td>
<td>Pravastatin</td>
</tr>
<tr>
<td>Serum markers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>6.29±0.52</td>
<td>6.37±0.73</td>
<td>5.28±0.65</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>4.31±0.49</td>
<td>4.31±0.70</td>
<td>3.22±0.65</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.46±0.31</td>
<td>1.54±0.34</td>
<td>1.56±0.34</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.32±0.41</td>
<td>1.37±0.48</td>
<td>1.25±0.51</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>4.55±0.33</td>
<td>4.55±0.33</td>
<td>4.66±0.33</td>
</tr>
<tr>
<td>Creatinine, mmol/L</td>
<td>80±8.8</td>
<td>80±8.8</td>
<td>80±8.8</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>140±3</td>
<td>140±2</td>
<td>140±2</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>4.1±0.3</td>
<td>4.2±0.2</td>
<td>4.2±0.2</td>
</tr>
<tr>
<td>Urine amino acids, mmol/L</td>
<td>0.35±0.04</td>
<td>0.34±0.05</td>
<td>0.34±0.04</td>
</tr>
<tr>
<td>Glu transaminase, IU/L</td>
<td>20±5</td>
<td>20±6</td>
<td>21±5</td>
</tr>
<tr>
<td>GP transaminase, IU/L</td>
<td>18±6</td>
<td>21±8</td>
<td>24±12</td>
</tr>
<tr>
<td>γ-Glutamyl transferase, IU/L</td>
<td>18±8</td>
<td>19±8</td>
<td>19±9</td>
</tr>
<tr>
<td>Creatine phosphokinase, IU/L</td>
<td>99±48</td>
<td>108±44</td>
<td>103±35</td>
</tr>
<tr>
<td>PRA, pmol Al·min⁻¹·L⁻¹</td>
<td>11.5±11.0</td>
<td>12.0±12.6</td>
<td>10.7±13.9</td>
</tr>
<tr>
<td>Plasma aldosterone, pmol/L</td>
<td>569±197</td>
<td>596±172</td>
<td>533±194</td>
</tr>
<tr>
<td>Plasma endothelin-1, pg/mL</td>
<td>4.5±2.1</td>
<td>4.0±1.8</td>
<td>2.9±1.4</td>
</tr>
<tr>
<td>Urinary aldosterone, pmol/min</td>
<td>31.4±13.5</td>
<td>31.0±13.3</td>
<td>27.9±10.8</td>
</tr>
<tr>
<td>Urinary sodium, μmol/min</td>
<td>84±37</td>
<td>86±28</td>
<td>84±27</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.8±4.2</td>
<td>25.6±4.0</td>
<td>25.6±4.0</td>
</tr>
</tbody>
</table>

$GO$ indicates glutamic oxalacetic; $GP$, glutamic pyruvic; $PRA$, plasma renin activity; $Al$, angiotensin; and $\Delta$, difference for pravastatin vs placebo. $P$ values are for comparison for pravastatin vs placebo. $n=25$ participants.
Table 2. Effect of Pravastatin on Blood Pressure

<table>
<thead>
<tr>
<th>Blood Pressure, mm Hg</th>
<th>Baseline</th>
<th>Placebo</th>
<th>Pravastatin</th>
<th>Δ (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>149±6</td>
<td>149±6</td>
<td>141±5</td>
<td>−8 (−10, −6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Pravastatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diastolic</strong></td>
<td>97±2</td>
<td>96±2</td>
<td>91±4</td>
<td>−5 (−7, −4)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Pulse</strong></td>
<td>52±2</td>
<td>53±2</td>
<td>50±4</td>
<td>−3 (−5, −0.7)</td>
<td>0.011</td>
</tr>
<tr>
<td><strong>CPT</strong>*</td>
<td>13±5</td>
<td>14±7</td>
<td>10±6</td>
<td>−4 (−7, −1)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

The per protocol analyses include only the patients who completed the trial. Intention-to-treat analyses include all the patients who did and did not drop out from treatment during the trial.

Δ indicates difference for pravastatin vs placebo.

*Increase in mean blood pressure compared with resting values.

Participants in whom it increased by 1 and 2 mm Hg, respectively. Diastolic pressure decreased in all participants by 0.3 to 12.5 mm Hg, except for 3 participants in whom it increased by 1 and 2 mm Hg, respectively. Diastolic pressure decreased in all participants by 0.3 to 12.5 mm Hg, except for 3 participants in whom it increased by 1 and 2 mm Hg, respectively.

The difference in blood pressure between pravastatin and placebo reached statistical significance after 4 weeks of follow-up for diastolic pressure and after 12 weeks for systolic pressure (−2 mm Hg, 95% CI −3 to −0.2, P=0.025, and −5 mm Hg, 95% CI −7 to −3, P=0.001). In the group initially assigned to pravastatin, after 16 weeks of crossover placebo, both systolic and diastolic blood pressures returned to pretreatment values, which showed that there was no carryover effect (Figure). Placebo treatment had a slight effect on blood pressure after week 0. The effects of pravastatin on blood pressure were virtually unchanged in intention-to-treat analyses that included the 5 patients who dropped out from the study treatment (Table 2) and in separate analyses stratified according to gender and age (<55 and ≥55 years) (data not shown). Within the pravastatin and placebo groups, neither systolic nor diastolic blood pressure was significantly correlated with total cholesterol, LDL cholesterol, HDL cholesterol, or plasma or urinary aldosterone levels (data not shown).

In separate analyses, we compared at week 16 the participants who initially were randomized to pravastatin with those initially randomized to placebo as in a traditional trial with 2 independent arms (Figure). In such analyses, systolic and diastolic blood pressures and total and LDL cholesterol levels were significantly decreased in the pravastatin group compared with placebo (P=0.001 for all comparisons).

At baseline, the cold pressor test increased mean blood pressure by 13±5 mm Hg (Table 2). The cold pressor test increased mean blood pressure by 14±7 mm Hg in the placebo group and 10±6 mm Hg in the pravastatin group. Therefore, the difference in blood pressure response after the cold pressor test between pravastatin and placebo was 4 mm Hg (P=0.005).

Circulating endothelin was reduced after pravastatin (P=0.001) (Table 1), although it must be noted that our basal values for endothelin were higher than those usually reported in the literature. The levels of circulating endothelin did not correlate with systolic or diastolic blood pressure or with blood pressure after the cold pressor test in either the pravastatin or placebo group.

Discussion

In our selected population, the HMG-CoA reductase inhibitor pravastatin significantly decreased systolic, diastolic, and pulse pressures and blunted the blood pressure increase induced by the cold pressor test. To the best of our knowledge, this is the first controlled trial that clearly demonstrated that a HMG-CoA reductase inhibitor could reduce both resting and stress-induced blood pressure in essential hypertensive patients with primary hypercholesterolemia.

Previous studies have found blood pressure–lowering effects of statins. In 2 experimental studies, both pravastatin and lovastatin significantly decreased mean arterial pressure in hypertensive rats after a few weeks of treatment. In 26 healthy normotensive individuals with high plasma cholesterol levels, compared with pretreatment values, 6 weeks of treatment with lovastatin blunted the systolic blood pressure increase triggered by the mental arithmetic test. RESTING systolic blood pressure was also decreased (but not significantly) by 3 mm Hg. In 2 other open-label studies in 49 and 23 hypertensive patients with hypercholesterolemia, fluvastatin significantly decreased systolic and diastolic blood pressures after 12 weeks compared with pretreatment values. In a randomized, double-blind, placebo-controlled crossover trial in 7 patients with mild hypertension, treatment with pravastatin blunted the diastolic blood pressure increase induced by angiotensin II and norepinephrine. No significant effect was found on systolic pressure. In an observational study in 127 hypertensive patients with hypercholesterolemia, the use of pravastatin or simvastatin in combination with various antihypertensive agents was associated with a greater reduction in both systolic and diastolic pressure than antihypertensive treatment alone (C. Borghi, oral communication, 1999). Other studies that included either normotensive individuals or hypertensive patients in whom blood pressure was controlled failed to find a blood pressure–lowering effect of statins. These findings suggest that similar to most antihypertensive agents, statins may decrease elevated but not normal blood pressure. A blood pressure reduction with statins may be difficult to detect in large event trials such as the West of Scotland Coronary Prevention Study or the Scandinavian Simvastatin Survival Study. In those trials, the potential effect on blood pressure was likely diluted by the large proportion of normotensive participants, in whom statins do not seem to affect blood pressure, and by the likely greater use of antihypertensive medications during the trials.
agents in the placebo group among those who had hypertension. In the present study, the antihypertensive effect of pravastatin was not affected by changes in body mass index, urinary sodium excretion, or plasma renin activity; these variables remained stable throughout the randomized phase of the trial. Systolic and diastolic blood pressures declined gradually after pravastatin and conversely increased again after discontinuation of therapy. These changes did not parallel the changes in serum lipids. We may only speculate that this fairly slow mechanism could be related to the possible restoration of endothelial function produced by pravastatin over the long term, as discussed below.

This antihypertensive effect of pravastatin was also independent of the dose of pravastatin, because the reduction of blood pressure observed in the patients who received 40 mg was similar to that observed in patients treated with 20 mg. HMG-CoA reductase inhibitors may cause vasodilation and a decrease in blood pressure by restoring the endothelial dysfunction that frequently accompanies hypertension and hypercholesterolemia.4–7 This interpretation is supported by the favorable effect of pravastatin on the cold pressor test and by the reduction in levels of circulating endothelin-1 after pravastatin. Other studies27,28 have shown that the blood pressure increase caused by the cold pressor test is associated with an increase in circulating cell adhesion molecules and endothelin. In the present study, measures of biological markers of endothelial function other than endothelin-1 were not available. The beneficial effect of pravastatin on blood pressure can be mediated not only by a decrease in LDL cholesterol1 but also by the upregulation of nitric oxide synthase.4,5

The hypothesis that clinical benefits of pravastatin unexplained by cholesterol lowering result from a nonlipid mechanism of endothelial nitric oxide synthase activation, resulting in increased nitric oxide release, was recently tested.29 Nitric oxide is a vasodilator and a potent inhibitor of platelet aggregation.30

In the present study, pravastatin significantly reduced circulating levels of endothelin-1, thus further supporting the hypothesis of a possible positive effect of statins on endothelial function. On the other hand, our baseline values of plasma endothelin-1 were higher than those usually reported in the literature. The levels of circulating endothelin-1 did not correlate with systolic or diastolic blood pressure or with blood pressure after the cold pressor test in either the pravastatin or the placebo group.

Pravastatin decreased both blood pressure and cholesterol levels, but the blood pressure reduction was not correlated with changes in plasma cholesterol level. This suggests that other mechanisms not mediated by cholesterol reduction were important.12 A reduction in plasma aldosterone with statins, reported by others,31 may have also played a role in the decrease in blood pressure. In the present study, pravastatin tended to decrease aldosterone levels, although not significantly, and in each treatment group, aldosterone levels were not significantly correlated with blood pressure changes.

Carryover effects may be a concern in crossover trials. In the present study, after treatment crossover, blood pressure and cholesterol levels were not affected by carryover effects of the initial regimen into the second phase of the trial. In the participants who initially received pravastatin, systolic and diastolic blood pressures and total and LDL cholesterol values returned to baseline values after the second placebo phase (Figure). Among those who initially received placebo, the magnitude of blood pressure and cholesterol reduction during the subsequent pravastatin phase was similar to that found in the group who initially received pravastatin.

Although blood pressure and cholesterol level decreased significantly during the first 8 weeks of run-in placebo, only minimal and nonsignificant changes were found during the subsequent 16 weeks in the group who initially received placebo. The findings of the trial are strengthened by the analyses performed at week 16, in which participants who initially were randomized to pravastatin were compared with those initially randomized to placebo, as in a traditional trial with 2 independent arms. Such analyses are not affected by carryover effects and confirmed that pravastatin significantly reduced blood pressure.

The effect of pravastatin on blood pressure observed in the present study has not been reported previously by the larger trials of pravastatin, such as LIPID, CARE, and WOSCOPS, in which >40% of the participants reported a history of hypertension.32 In any case, such conflicting evidence could be explained by the fact that those trials were not specifically designed to assess the effects of pravastatin on blood pressure, and all the hypertensive patients were taking antihypertensive treatment, as stated above.

The generalizability of the present findings is limited by the selection of the participants and by the limited duration of the trial. With a 16-week follow-up period for patients receiving placebo, there is no ethical concern about withholding antihypertensive treatment from patients with mild-to-moderate hypertension, even in the presence of moderately high cholesterol values.

Additional studies are needed to assess whether HMG-CoA reductase inhibitors decrease blood pressure over a longer period of time in patients with comorbid conditions and higher baseline blood pressure and cholesterol levels, as well as in patients undergoing antihypertensive treatment. It is not known whether all statins are equally effective in reducing blood pressure or whether certain statins might interact with other antihypertensive agents.

In conclusion, the present trial shows that the magnitude of the blood pressure reduction achieved with the HMG-CoA reductase inhibitor pravastatin is likely clinically relevant.33,34 The slight yet clear antihypertensive effect shown by pravastatin after a few weeks in untreated hypertensives with primary hypercholesterolemia may contribute to the health benefits of statins achieved in large randomized trials and may account in part for the early reduction in adverse events.

Acknowledgments

This study was supported by a grant of the Ministero della Università e Ricerca Scientifica e Tecnologica (60%) and by a grant from Bristol Myers Squibb, Italy.

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Hypertension. 1999;34:1281-1286
doi: 10.1161/01.HYP.34.6.1281

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