Plasma Lipoprotein Levels in Treated and Untreated Hypertensive Men and Women

The National Heart Foundation of Australia Risk Factor Prevalence Study

Stephen W. MacMahon, Graham J. Macdonald, and Ralph B. Blacket

Experimental studies have reported that common antihypertensive drugs such as diuretics, beta-blockers, and methyldopa have adverse effects on plasma lipids and lipoproteins. To investigate whether such effects can be observed in the general population, plasma lipid and lipoprotein levels were compared in subjects receiving antihypertensive treatment, subjects with untreated high blood pressure, and subjects with normal blood pressure in a random sample of 5603 subjects screened in a national study of risk factor prevalence in Australia. In both sexes, high density lipoprotein (HDL) cholesterol was lower in the group receiving treatment than in the others (p < 0.001). In men, triglycerides (TG) (p < 0.001) and the ratio of total cholesterol to HDL cholesterol (TC/HDL cholesterol) (p < 0.05) were higher in the group receiving treatment. In both sexes, the differences in plasma lipids and lipoproteins between treated and untreated hypertensive groups were independent of age, body mass index, alcohol consumption, and smoking. More than 40% of the treated or untreated hypertensive men and women had elevated total cholesterol (TC > 252 mg/dl) or an elevated TC/HDL cholesterol ratio (>6.0). In men receiving antihypertensive treatment, the prevalence of an elevated TC/HDL cholesterol ratio was significantly greater than in men with untreated high blood pressure (p < 0.01). The results of this study suggest that the effects of antihypertensive treatment on plasma lipids and lipoproteins can be observed in population lipid and lipoprotein levels. Even before treatment, a large proportion of high blood pressure patients have a significant plasma cholesterol abnormality, which may be aggravated by conventional antihypertensive therapy. (Arteriosclerosis 5:391-396, July/August 1985)

High blood pressure is an important risk factor for coronary artery disease. The failure of antihypertensive treatment to produce the expected reductions in morbidity and mortality from coronary artery disease has stimulated interest in the possibility that antihypertensive drugs may adversely affect other risk factors, such as plasma lipids and lipoproteins, and thus offset the benefit of reducing blood pressure. Experimental studies have reported that both thiazide and loop diuretics may increase total cholesterol (TC), low density lipoprotein (LDL) cholesterol and triglycerides (TG). Both selective and nonselective beta-blockers decrease high density lipoprotein (HDL) cholesterol and increase TG. When beta-blockers and diuretics are given concurrently, HDL cholesterol is decreased and TG is increased, but there is no increase in total cholesterol or LDL cholesterol. Decreases in HDL cholesterol have also been reported after treatment with methyldopa. The changes in plasma lipid and lipoprotein levels associated with antihypertensive treatment have been shown to significantly offset the reduction in the calculated risk of coronary artery disease (CAD) that results from blood pressure reduction.

Most studies of the effects of antihypertensive treatment on plasma lipids and lipoproteins have included...
volved small numbers of subjects and short follow-up
tervals. In the Multiple Risk Factor Intervention Tri-
oral, however, there were significant reductions in
HDL cholesterol and increases in TG in a large group
of subjects treated with the beta-blocker propranolol
after 72 months of treatment. These results suggest
that in populations in which beta-blockers are used
widely to treat hypertension, the plasma lipid and
lipoprotein changes associated with treatment may
be of sufficient duration and magnitude to affect
mean plasma lipid and lipoprotein levels and the
population risk of CAD in community hypertensive
groups.

In the present study, we examined a random sam-
ple of men and women living in Australian urban
communities who were receiving antihypertensive
therapy and compared their plasma lipid and lipopro-
tein levels with those of normotensive and untreated
hypertensive subjects from the same population. We
took account of factors such as age, body mass
index, alcohol consumption, and smoking that might
confound the comparison. National statistics on
pharmaceutical prescriptions indicate that in 1980,
the year of this study, approximately 35% of pre-
scriptions for antihypertensive treatment were for
beta-blockers, 15% were for methyldopa, and 40%
were for diuretics. The changes in plasma lipids and
lipoproteins reported in studies of regimens using
these drugs suggest that a random sample of Aus-
tralian patients receiving antihypertensive therapy
would have lower HDL cholesterol and higher TG
levels than comparable groups not receiving ther-
apy. Depending on the frequency of diuretic mono-
therapy and the duration of the therapy’s effects on
plasma lipids and lipoproteins, there might also be
higher TC and LDL cholesterol levels in the treated
group.

Methods

The Risk Factor Prevalence Study was conducted
from May to November 1980 in the six state capital
cities of Australia. The study population was a ran-
dom sample from the electoral rolls of people aged
25 to 64 years. Informed consent was given by all
participants. There were 5603 subjects, 2765 men
and 2838 women, representing a response rate of
75.7%. Comparison of the demographic characteris-
tics and age structure of the study population with
census data for the same age group in the same
geographic locations revealed few differences. A
full account of the methods and a preliminary analy-
sis of the data has been published.

All subjects filled out a dietary and medical history
questionnaire and a medical examination. Subjects
were asked whether or not they were receiving anti-
hypertensive therapy, but information about the spe-
cific type of treatment was not recorded. Blood pres-
sure was measured by observers using standard
mercury sphygmomanometers and cuffs who had
been trained in a common protocol similar to that of
the Lipid Research Clinics Prevalence Study. Systo-
tic and diastolic (phase V) blood pressures were
defined as the mean of two readings taken consecu-
tively in the seated position after a 5-minute rest with
the cuff on the right arm. High blood pressure was
arbitrarily defined as a diastolic blood pressure of 95
mm Hg or more and/or a systolic blood pressure of
150 mm Hg or more. Resting heart rate in beats per
minute (bpm) was recorded from the radial pulse.

Plasma lipids and lipoproteins were also mea-
sured by the Lipid Research Clinics method. All
participants had fasted for at least 12 hours. Using
the criteria of the National Heart Foundation of Aus-
tralia, we defined hypercholesterolemia as a TC of
252 mg/dl (6.5 mmol/liter) or greater; in both men
and women, this level approximated the 80th per-
centile in the distributions of TC. On the basis of the
Framingham Study data, elevated TC/HDL choles-
terol was defined as a ratio of 6.0 or more.

Adiposity was assessed by using Quetelet’s body
mass index [weight(kg)/height(m)²]. Alcohol intake
was assessed from the subjects’ estimate of the usu-
al frequency of drinking (number of days per week)
and the usual number of drinks consumed on each
day. Subjects were asked whether they currently
smoked. Excluded were 419 subjects who had not
fasted or from whom insufficient blood was taken,
and 351 women who were pregnant or taking oral
contraceptives.

Differences between groups in blood pressure,
heart rate, plasma lipid and lipoprotein levels, and
the prevalence of plasma lipid abnormalities were
tested using t tests, analysis of covariance, and chi-

<table>
<thead>
<tr>
<th>Table 1. Age, Blood Pressure, and Heart Rate</th>
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</thead>
<tbody>
<tr>
<td>Normal blood pressure</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td>Age (yrs)</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
</tr>
<tr>
<td>HR (bpm)</td>
</tr>
</tbody>
</table>

Values represent means ± sd. SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate.
Table 2. Plasma Lipid and Lipoprotein Concentrations and Ratios

<table>
<thead>
<tr>
<th></th>
<th>Normal blood pressure</th>
<th>High blood pressure</th>
<th>Difference between normal &amp; high BP</th>
<th>On antihypertensive drugs</th>
<th>Difference between high BP &amp; on drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-C</td>
<td>219</td>
<td>227</td>
<td>p&lt;0.001</td>
<td>226</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-C</td>
<td>146</td>
<td>148</td>
<td>NS</td>
<td>147</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-C</td>
<td>48</td>
<td>48</td>
<td>NS</td>
<td>45</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>T-C/HDL-C</td>
<td>4.79</td>
<td>5.01</td>
<td>p&lt;0.01</td>
<td>5.96</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Tg</td>
<td>125</td>
<td>138</td>
<td>p&lt;0.001</td>
<td>165</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-C</td>
<td>219</td>
<td>230</td>
<td>p&lt;0.001</td>
<td>227</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-C</td>
<td>143</td>
<td>152</td>
<td>p&lt;0.001</td>
<td>149</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-C</td>
<td>59</td>
<td>58</td>
<td>NS</td>
<td>56</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>T-C/HDL-C</td>
<td>3.95</td>
<td>4.21</td>
<td>p&lt;0.001</td>
<td>4.26</td>
<td>NS</td>
</tr>
<tr>
<td>Tg</td>
<td>87</td>
<td>102</td>
<td>p&lt;0.001</td>
<td>110</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: T-C = total cholesterol; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; T-C/HDL-C = ratio of total cholesterol to high density lipoprotein cholesterol; Tg = total triglycerides; NS = not statistically significant (p > 0.05).

square analysis. Using data from the Framingham Study, we estimated the effect of differences in blood pressure and plasma lipoproteins on the risk of CAD.

**Results**

In this study population, 8% of the men and 13% of the women were receiving antihypertensive treatment; a further 22% of the men and 14% of the women had a diastolic blood pressure of 95 mm Hg or more or a systolic blood pressure of 150 mm Hg or more (Table 1). Men and women receiving antihypertensive treatment had lower systolic and diastolic blood pressures than those with high blood pressure not on treatment (p < 0.001), but higher blood pressures than normal (p < 0.001). Heart rates were greater in the group with high blood pressure compared to the group with normal blood pressure (p < 0.001); heart rates were lower in the group on antihypertensive treatment compared with the high blood pressure group not being treated (p < 0.001).

Age, body mass index, alcohol consumption, and smoking are associated with plasma lipid and lipoprotein levels. Table 2 presents mean plasma lipid and lipoprotein levels with the linear adjustment by analysis of covariance for age, body mass index, alcohol consumption, and smoking. To take account of the sharp increase in TC, LDL cholesterol and TG in women over age 50, these levels were adjusted for age. In both sexes, TC, Tg, and HDL cholesterol ratio and TG were higher in subjects with treated or untreated high blood pressure than in subjects with normal blood pressure. In women, LDL cholesterol was also greater in subjects with untreated high blood pressure than in subjects with normal blood pressure. In both sexes, TC, HDL cholesterol ratio and TG were higher in subjects with treated high blood pressure than in subjects with untreated high blood pressure. In women, HDL cholesterol was similar in normal and untreated high blood pressure groups; in subjects receiving treatment for high blood pressure, HDL cholesterol was lower than in subjects with untreated high blood pressure. In men, TC/HDL cholesterol ratios and TG were higher in those receiving antihypertensive treatment than in those without treatment. The differences in HDL cholesterol, TC/HDL cholesterol ratios and TG between the three groups persisted when considered separately for systolic (>150 mm Hg) and diastolic (>95 mm Hg) blood pressure elevations.

Table 3 shows the unadjusted prevalence of elevated TC (>252 mg/dl) and elevated TC/HDL cholesterol ratios (>6.0) in normotensive and hypertensive groups in the study population.
The differences between treated and untreated hypertensive groups suggest that the effects on HDL cholesterol and TG of antihypertensive therapy, as practiced in Australia, are of sufficient magnitude and duration to affect the mean plasma lipid and lipoprotein levels of treated hypertensive groups in the community. These results are consistent with the Lipid Research Clinics’ observation of a lower HDL cholesterol level and a higher TG level in the small group of subjects receiving propranolol in comparison with matched controls from the same study population.31 Our finding of similar levels of TC and LDL cholesterol in treated and untreated hypertensive subjects suggests that: 1) diuretics were most often prescribed in conjunction with beta-blockers, which prevent the increase in TC and LDL cholesterol normally associated with diuretic therapy;16 or 2) the effects of diuretic monotherapy on TC and LDL cholesterol are not of sufficient magnitude or duration to significantly affect population lipid or lipoprotein levels.

It is possible to estimate the overall effects that antihypertensive treatment may have had on the risk of CAD in these subjects by using data from the Framingham Study about the risk of developing CAD at different blood pressure and plasma lipoprotein cholesterol levels. In the Framingham Study, the risk of coronary artery disease in men with “borderline hypertension” (a systolic blood pressure of 140–159 mm Hg and/or a diastolic blood pressure of 90–95 mm Hg), was 18% less than in men with “established hypertension” (systolic blood pressure of 160 mm Hg or more and/or a diastolic blood pressure greater than 95 mm Hg); in women, the risk was 29% less in the borderline hypertension group.25 In the present study, the blood pressures of subjects treated for high blood pressure closely approximated those of the Framingham borderline hypertension group; pretreatment blood pressures in this group were probably similar to those of the established hypertension group. If lowering blood pressure from established hypertension levels to borderline hypertension levels reduces the risk of CAD to the level associated with the lower blood pressure, then antihypertensive treatment in our subjects may have reduced the risk of CAD by 18% in men and 29% in women. (This assumes that all other risk factor levels remain constant.)

Using similar data from the Framingham Study about CAD risk associated with different levels of HDL cholesterol, we estimated that for both sexes, the 5% lower HDL cholesterol level in subjects being treated for high blood pressure increased the CAD risk associated with this lipoprotein by 12%.26 Therefore in men, who have most of the coronary events, approximately two-thirds of the estimated reduction in risk associated with lowering blood pressure could be offset by a 5% decrease in HDL cholesterol. In women, at least 40% of the reduction in risk associated with lowering blood pressure could be offset by such a decrease in HDL cholesterol. While these
effects on the calculated risk of CAD warrant concern, work is still required to determine the true significance of drug-induced changes in plasma lipids and lipoproteins.

The importance of considering plasma lipid and lipoprotein changes during antihypertensive therapy is accentuated by our finding that, even before treatment, more than 40% of all hypertensive subjects had a TC higher than 252 mg/dl or a TC/HDL cholesterol ratio higher than 6.0. The tendency for persons with high blood pressure to have high plasma lipid levels has also been observed in studies from the United States and Norway. However, it is not widely recognized that almost one in two patients with high blood pressure will probably have a significant plasma cholesterol abnormality. In men in our study who received antihypertensive treatment, abnormalities of plasma lipid and lipoprotein cholesterol occurred with even greater frequency than in men with untreated high blood pressure. In men on treatment, more than 50% had elevated TC levels or TC/HDL cholesterol ratios.

The results of the present study indicate that a large proportion of persons with untreated high blood pressure probably have a plasma lipid or lipoprotein cholesterol abnormality, and that such abnormalities may be aggravated by antihypertensive therapy. This suggests that there is a strong case for the routine investigation of plasma lipid and lipoprotein levels in high blood pressure patients before and during antihypertensive treatment. In patients with pre-existing plasma lipid or lipoprotein abnormalities or in patients whose plasma lipid levels react adversely to conventional antihypertensive therapy, it seems reasonable to consider therapeutic agents without known adverse effects on plasma lipids or lipoproteins. In addition, lipid-modifying diets, which reverse some of the plasma lipid and lipoprotein changes associated with antihypertensive treatment, should be prescribed. The criteria for successful treatment of high blood pressure should include the absence of adverse effects on plasma lipid and lipoprotein levels.

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