The Hypertensive Patient With Multiple Risk Factors
Is Treatment Really So Difficult?

Alberto Zanchetti

Multiple risk factors for cardiovascular disease, particularly hypercholesterolemia, are often present in the hypertensive patient. Recent guidelines, ranging from those prepared by the World Health Organization/International Society of Hypertension to those of the three European Societies of Cardiology, Atherosclerosis, and Hypertension, stress the importance of evaluating global risk, based on the presence of all cardiovascular risk factors in an individual or in a group of subjects.

It has also been suggested that treatment should aim to correct all modifiable risk factors. This is a reasonable recommendation, but although observational epidemiologic studies have shown that the effects of concomitant risk factors are additive, if not multiplicative, it is surprising that no intervention trial has been undertaken to determine whether the benefits of treating more than one risk factor are also additive.

The Plaque Hypertension Lipid-Lowering Italian Study (PHYLLIS) is the first such study. Its aim is to investigate the potential benefit of lowering blood pressure and plasma cholesterol on the progression of carotid plaque in hypertensive patients with elevated plasma cholesterol. Using a factorial design, the antiatherosclerotic effect of two different antihypertensive drugs, the angiotensin-converting enzyme (ACE) inhibitor fosinopril and the diuretic hydrochlorothiazide will be compared. The study aims to confirm animal experiments demonstrating the benefit of ACE inhibitors on experimental atherosclerosis. PHYLLIS will also compare the effects of two lipid-lowering regimens, diet plus placebo and diet plus pravastatin, in the study population. This 3-year, multicenter, double-blind, randomized Italian study, using B-mode ultrasound evaluation of the carotid walls with central reading of the ultrasound scans (Bowman Gray University, Winston-Salem, NC) is now underway and should provide useful evidence about the benefits of multiple risk factor treatment in the hypertensive patient. Am J Hypertens 1997;10:223S–229S © 1997 American Journal of Hypertension, Ltd.

KEY WORDS: Hypertension, hypercholesterolemia, fosinopril, hydrochlorothiazide, pravastatin.

Hypertension is often found in association with multiple metabolic derangements, principally hypercholesterolemia. The absolute prevalence of this association is somewhat variable, depending on the definition used. Both cholesterol and blood pressure are continuous variables in the population, and therefore the level set for the blood pressure threshold for hypertension or the cholesterol threshold for hypercholesterolemia affects prevalence statistics.

From the Centro di Fisiologia Clinica e Ipertensione and Istituto di Clinica Medica, University of Milan and Ospedale Maggiore and Istituto Auxologico Italiano, Milan, Italy.

Address correspondence and reprint requests to Professor Alberto Zanchetti, Centro Fisiologia Clinica e Ipertensione, Ospedale Policlinico, Via F. Sforza 35, 20122 Milano, Italy.
Table 1, taken from a recent paper by Goode et al., summarizes results from various population surveys, comprising more than 40,000 subjects. Highly significant correlations were found in all studies between the blood pressure values and total cholesterol, triglycerides, or low-density lipoprotein (LDL) cholesterol. Therefore, even in healthy populations, it appears that there is some correlation between blood pressure and serum cholesterol or triglycerides.

A recent epidemiologic survey in Gubbio, a small town in central Italy, where the entire population was screened for high blood pressure and other risk factors associated with cardiovascular disease, provides some additional data. Figure 1 illustrates the prevalence of hypercholesterolemia (defined as a total plasma cholesterol of ≥250 mg/dL) in normotensive and hypertensive subjects in the Gubbio population. The threshold for hypertension was defined as 160 mm Hg systolic or 95 mm Hg diastolic blood pressure. The survey found that hypercholesterolemia was more prevalent among hypertensive men than among normotensive men (≥75 years). The same was true for women. The prevalence of hyperglycemia was also higher in both male and female hypertensive subjects, particularly in older individuals (Figure 2). When all risk factors for cardiovascular disease, including cigarette smoking, were taken into account, almost 90% of the hypertensive population in Gubbio had at least one additional risk factor for cardiovascular disease, thus confirming the clustering of cardiovascular risk factors in hypertensive patients.

Table 2 provides data from the San Antonio study, a similar survey of cardiovascular risk factors in the population of San Antonio, Texas. In this study, hypertension was present in about 10% of the population, but only 1.5% had an isolated increase in blood pressure, whereas 56% of the hypertensive subjects had at least three risk factors in addition to high blood pressure.

### Table 1. Epidemiologic Relationship Between Blood Pressure and Serum Lipids

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Subjects</th>
<th>Lipid Fraction Positively Associated With Blood Pressure</th>
<th>Correlation Coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tecumseh Community Health</td>
<td>3064</td>
<td>Total cholesterol</td>
<td>0.16 SBP</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Triglycerides</td>
<td>0.18 SBP</td>
<td></td>
</tr>
<tr>
<td>Southern California</td>
<td>4839</td>
<td>Total cholesterol + triglycerides</td>
<td>0.28 SBP</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Lipid Research Clinics</td>
<td>7747</td>
<td>Triglycerides + VLDL cholesterol†</td>
<td>Not given</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Program Prevalence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Framingham</td>
<td>5127</td>
<td>Total cholesterol</td>
<td>0.15 SBP; 0.20 DBP</td>
<td>Not given</td>
</tr>
<tr>
<td>Tromso</td>
<td>16,744</td>
<td>Total cholesterol</td>
<td>0.19 SBP</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-HDL cholesterol</td>
<td>0.25 DBP; 0.13 SBP</td>
<td></td>
</tr>
<tr>
<td>Zavaroni et al</td>
<td>64</td>
<td>Triglycerides</td>
<td>Not given</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Williams et al</td>
<td>6218</td>
<td>LDL cholesterol</td>
<td>Not given</td>
<td>&lt;.0001†</td>
</tr>
</tbody>
</table>

* Excess of hypertension in IIB and IV phenotypes.
† Significant aggregation of lipid abnormalities in 58 families with familial dyslipidemic hypertension.

VLDL, very low-density lipoprotein; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure.

From Goode et al.2

Global Assessment of Cardiovascular Risk and Intervention Guidelines

The multiple clustering of metabolic abnormalities in hypertension or other risk factors for cardiovascular disease should be considered important for prognosis, diagnosis, and therapy. The importance of a global assessment of cardiovascular risk in patients with hypertension was emphasized in the 1993 guidelines for the management of hypertension, issued by the World Health Organization (WHO)/International Society of Hypertension (ISH) Mild Hypertension Liaison Committee. The guidelines state, “Among individuals with mild hypertension the risk of serious cardiovascular disease is also determined by a variety of factors other than the level of blood pressure... The presence of one or more risk factors may be a more important determinant of risk than a mild increase in the level of blood pressure. Since the absolute benefit of antihypertensive treatment will be determined by the absolute risk of cardiovascular disease (ie, greater benefits among those at higher risk), each of these factors should be assessed prior to making the decision about treatment.”

When discussing intervention, the WHO/ISH guidelines state that, “Since high serum cholesterol levels and diabetes also unfavourably influence the long-term prognosis of hypertensive people, nutritional counselling and, when appropriate, drug treatment, are indicated to control these risk factors.”

The importance of assessing overall risk when making intervention decisions is given particular emphasis.
in the 1994 recommendations for the prevention of coronary heart disease issued by the three European Societies of Cardiology, Atherosclerosis, and Hypertension. A risk chart indicating the overall absolute risk of cardiovascular disease, taking into consideration gender, age, total serum cholesterol, systolic blood pressure, and smoking, is shown in Figure 3. The recommendations for intervention are based on the absolute risk: the higher the risk; the more stringent the recommendations for intervention.

In spite of these recommendations and of numerous trials of antihypertensive therapy, it is somewhat surprising that the real benefits of treating multiple risk factors have never been investigated in a formal trial, with the exception of the Multiple Risk Factor Intervention Trial (MRFIT) some years ago in the United States, which was not a great success.

Despite very considerable progress in understanding the mechanisms of hypertension-related vascular damage, assessment of the treatment benefits of antihypertensive therapy has so far been based exclusively on randomized trials monitoring cardiovascular events. These trials have provided a great deal of important information, but many aspects of antihypertensive treatment still need further investigation, for example, the effectiveness of antihypertensive treatment on preventing hemorrhagic, thrombotic, and lacunar stroke, and the definition of the types of cardiac damage that can be prevented. The evidence shows that hypertension is an important risk factor for the development of atherosclerosis, but whether antihypertensive therapy can prevent some of the effects of atherosclerosis (such as stroke or myocardial infarction), or whether therapy can indeed prevent the development of atherosclerosis per se, are questions that remain unanswered.
Defining the relationship between antihypertensive treatment and the development of atherosclerosis has become crucial because much evidence has accumulated in recent years using various experimental models of atherosclerosis (Table 3),\textsuperscript{10,11} in which the effects of antihypertensive drugs have been tested. Favorable effects have been described particularly for two classes of antihypertensive drug—calcium antagonists and angiotensin converting enzyme (ACE) inhibitors.\textsuperscript{10,11}

Among the various animal models of atherosclerosis, the cholesterol-fed rabbit and the Watanabe genetically hyperlipidemic rabbit deserve special attention.

\begin{table}
\centering
\begin{tabular}{lcccccc}
\hline
 & Overall & NIDDM & IGT & HBP & HTG & HCH \\
\hline
Prevalence & 54.3 & 9.3 & 11.1 & 9.8 & 10.3 & 9.2 \\
Isolated & 29.1 & 1.3 & 1.8 & 1.5 & 1.0 & 1.8 \\
2 × 2 associations & & & & & & \\
NIDDM & 3.8 (5.1) & — & — & — & — & — \\
IGT & 4.6 (5.0) & — & — & — & — & — \\
HBP & 2.2 (5.3) & 0.1 (0.9) & 0.3 (1.1) & — & — & — \\
HTG & 3.0 (5.6) & 0.2 (1.0) & 0.2 (1.1) & 0.1 (1.0) & — & — \\
HCH & 2.4 (5.0) & 0.2 (0.9) & 0.1 (1.0) & 0.1 (0.1) & 0.5 (1.0) & — \\
Multiple associations & 17 & 40 & 37 & 56 & 51 & 45 \\
\hline
\end{tabular}
\caption{Prevalence Rates of Obesity, Type 2 (Non-Insulin Dependent) Diabetes (NIDDM), Hypertension (HBP), Impaired Glucose Tolerance (IGT), Hypertriglyceridemia (HTG), and Hypercholesterolemia (HCH) in 2930 Subjects in San Antonio, Texas}
\end{table}

Entries are actual crude prevalence rates (in percent). The numbers in parentheses are the expected prevalence rates of 2 × 2 associations, calculated as the product of the overall prevalence rates of the two numbers of the pair. The last line shows the percentage of all the cases of each condition occurring in combination of three or more with other conditions.

From Ferrannini et al\textsuperscript{4} with permission.

\section{Antihypertensive Treatment and Atherosclerosis}

Defining the relationship between antihypertensive treatment and the development of atherosclerosis has become crucial because much evidence has accumulated in recent years using various experimental models of atherosclerosis (Table 3),\textsuperscript{10,11} in which the effects of antihypertensive drugs have been tested. Favorable effects have been described particularly for two classes of antihypertensive drug—calcium antagonists and angiotensin converting enzyme (ACE) inhibitors.\textsuperscript{10,11}

Among the various animal models of atherosclerosis, the cholesterol-fed rabbit and the Watanabe genetically hyperlipidemic rabbit deserve special attention.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{coronary_risk_chart.png}
\caption{Coronary Risk Chart based on a risk function derived from the Framingham study, according to the recommendations of the European Society of Cardiology, European Atherosclerosis Society, and European Society of Hypertension. (From Pyörälä et al, with permission of W.B. Saunders Co., Ltd., London.)}
\end{figure}
In the former experimental model, drugs are administered to the animal in conjunction with a high cholesterol diet, and experiments test the capacity of the drugs to prevent or slow the development of atherosclerosis rather than treating preexisting atherosclerosis. The Watanabe genetically hyperlipidemic rabbit, in which there is a genetically determined deficiency of LDL receptors, starts to develop atherosclerosis in the fetus. When treatment is initiated a few weeks after birth, the animal is already atherosclerotic, thus offering a suitable model for testing the capacity of drugs to treat or modify atherosclerosis.11

Various calcium antagonists and β-blockers, such as propranolol, have been tested in the Watanabe rabbit, all with negative results.10 Only ACE inhibitors have been shown to induce regression or to slow the progression of preexisting atherosclerosis12,13 and therefore, are the only agents to date to show a therapeutic, rather than a preventive effect, on experimental atherosclerosis.

In the clinical setting, the antiatherosclerotic effects of antihypertensive drugs can now be explored using quantitative B-mode ultrasound measurement of the intima–media complex in the carotid artery wall.17 This technique can be used to assess whether some classes of antihypertensive agents, notably calcium antagonists or ACE inhibitors, exert a direct antiatherosclerotic effect in humans, in addition to the effects attributable to blood pressure reduction. An additional question, certainly relevant for the hypertensive patient with hypercholesterolemia, is whether more substantial antiatherosclerotic effects can be achieved when antihypertensive treatment is combined with lipid-lowering therapy.

### TABLE 3. EXPERIMENTAL MODELS OF ATHEROSCLEROSIS

| 1. Cholesterol-fed rabbits (or monkeys) |
| 2. Watanabe genetically hyperlipidemic rabbit |
| 3. Transgenic mouse model with Apo E deficiency |
| 4. Balloon catheter injury of arterial endothelium |
| 5. Intimal thickening to periarterial sheath |
| 6. Cell culture systems: |
| - a) Smooth muscle cell |
| - b) Fibroblasts |
| - c) Macrophages |
| 7. Ca\(^{2+}\) overload (vitamin D\(_3\)) |
| 8. Small artery disease in SHR and Dahl-S rats |

From Zanchetti,11 with permission.

In the clinical setting, the antiatherosclerotic effects of antihypertensive drugs can now be explored using quantitative B-mode ultrasound measurement of the intima–media complex in the carotid artery wall.17 This technique can be used to assess whether some classes of antihypertensive agents, notably calcium antagonists or ACE inhibitors, exert a direct antiatherosclerotic effect in humans, in addition to the effects attributable to blood pressure reduction. An additional question, certainly relevant for the hypertensive patient with hypercholesterolemia, is whether more substantial antiatherosclerotic effects can be achieved when antihypertensive treatment is combined with lipid-lowering therapy.

However, in experiments using the hyperlipidemic hamster, small doses of fosinopril were shown to be effective in early atherosclerosis without lowering arterial pressure. Another possible mechanism is inhibition of LDL oxidation. Additional possibilities include inhibition of smooth muscle cell hypertrophy and proliferation, inhibition of smooth muscle cell migration, inhibition of sympathetic activity, and an increase in vascular bradykinin or prostacyclin. However, it is still not known which mechanisms are responsible and whether the antiatherosclerotic action of ACE inhibitors, so clearly observed in animal models, also will be observed in humans.

In the clinical setting, the antiatherosclerotic effects of antihypertensive drugs can now be explored using quantitative B-mode ultrasound measurement of the intima–media complex in the carotid artery wall.17 This technique can be used to assess whether some classes of antihypertensive agents, notably calcium antagonists or ACE inhibitors, exert a direct antiatherosclerotic effect in humans, in addition to the effects attributable to blood pressure reduction. An additional question, certainly relevant for the hypertensive patient with hypercholesterolemia, is whether more substantial antiatherosclerotic effects can be achieved when antihypertensive treatment is combined with lipid-lowering therapy.

There is much speculation about possible mechanisms for the powerful antiatherosclerotic effect of ACE inhibitors in animal models.16 One such explanation relates to the lowering of arterial pressure.

However, in experiments using the hyperlipidemic hamster, small doses of fosinopril were shown to be effective in early atherosclerosis without lowering arterial pressure. Another possible mechanism is inhibition of LDL oxidation. Additional possibilities include inhibition of smooth muscle cell hypertrophy and proliferation, inhibition of smooth muscle cell migration, inhibition of sympathetic activity, and an increase in vascular bradykinin or prostacyclin. However, it is still not known which mechanisms are responsible and whether the antiatherosclerotic action of ACE inhibitors, so clearly observed in animal models, also will be observed in humans.

In the clinical setting, the antiatherosclerotic effects of antihypertensive drugs can now be explored using quantitative B-mode ultrasound measurement of the intima–media complex in the carotid artery wall.17 This technique can be used to assess whether some classes of antihypertensive agents, notably calcium antagonists or ACE inhibitors, exert a direct antiatherosclerotic effect in humans, in addition to the effects attributable to blood pressure reduction. An additional question, certainly relevant for the hypertensive patient with hypercholesterolemia, is whether more substantial antiatherosclerotic effects can be achieved when antihypertensive treatment is combined with lipid-lowering therapy.

There is much speculation about possible mechanisms for the powerful antiatherosclerotic effect of ACE inhibitors in animal models.16 One such explanation relates to the lowering of arterial pressure.
A number of studies are in progress to compare the effects of various antihypertensive drugs on the development of carotid atherosclerosis.\textsuperscript{16} The Multicentre Isradipine/Diuretic Atherosclerosis Study (MIDAS) was the pioneer in this field.\textsuperscript{18} As with many pioneering studies, it has highlighted some of the difficulties in undertaking clinical trials rather than providing answers, but an awareness of these problems has been valuable in designing later study protocols. The subjects included in the MIDAS trial were only mildly hypertensive (mean systolic blood pressure, 149 mm Hg; mean diastolic blood pressure, 96 mm Hg), and therefore, carotid lesion progression was quite slow. In addition, in future studies a more sensitive end-point than that used in the MIDAS trial should probably be assessed (ie, the mean of four sites at the bifurcations and in the distal carotids, rather than the mean of 12 sites along the carotid tree). Finally, longitudinal control of reading accuracy must be established.\textsuperscript{19}

THE PLAQUE HYPERTENSION LIPID-LOWERING ITALIAN STUDY

To discover the best therapy for the hypertensive, hypercholesterolemic patient with carotid atherosclerosis, recently we have begun recruitment for the Plaque Hypertension Lipid-Lowering Italian Study (PHYLLIS). The study will evaluate the efficacy of fosinopril or hydrochlorothiazide, with or without the addition of the lipid-lowering drug pravastatin, on the progression of carotid atherosclerosis, assessed by B-mode ultrasound imaging in hypercholesterolemic, hypertensive patients.\textsuperscript{20} The primary objectives of the study are to determine whether fosinopril is more effective than hydrochlorothiazide, whether pravastatin is more effective than a lipid-lowering diet, and whether combined antihypertensive treatment with fosinopril and lipid-lowering treatment with pravastatin is more effective than the other treatment regimens in slowing the progression of carotid artery atherosclerosis.

The PHYLLIS trial will include men and women, aged 45 to 70 years, with a seated diastolic blood pressure of 95 to 115 mm Hg, serum LDL cholesterol between 160 and 200 mg/dL, and at least one uncomplicated atherosclerotic lesion in the carotid arteries with an intima–media thickness of between 1.3 and 4.0 mm. A double-blind factorial design is being used, in which patients are randomized to antihypertensive treatment with either hydrochlorothiazide or fosinopril, and to a lipid-lowering diet with the addition of either placebo or pravastatin. The primary end-point of the PHYLLIS trial is the change in the mean intima–media thickness at four sites: the distal walls of the carotid bifurcations and the distal portion of the common carotid arteries. Treatment will continue for 3 years. The study is being conducted at several Italian hospitals, where patients are screened, carotid ultrasound scans and ambulatory blood pressure monitoring are performed, and treatment monitored. Central reading of carotid scans will be performed at the Bowman Gray School of Medicine (Winston-Salem, NC) and ambulatory blood pressure readings will be performed at the University of Milan (Milan, Italy). Recruitment began in 1996 and should be completed during 1997, with results available in the year 2000 (Figure 5).

<table>
<thead>
<tr>
<th>Patient selection (n=400)</th>
<th>Patient randomization (n=100/group)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males and females</td>
<td>Hydrochlorothiazide + Placebo fosinopril + Placebo pravastatin</td>
</tr>
<tr>
<td>Age 45–70 years</td>
<td>Fosinopril + Placebo hydrochlorothiazide + Placebo pravastatin</td>
</tr>
<tr>
<td>Seated DBP 95–115 mmHg</td>
<td>Hydrochlorothiazide + Placebo fosinopril + Pravastatin</td>
</tr>
<tr>
<td>Serum LDL cholesterol 160–200 mg/dl</td>
<td>Fosinopril + Placebo hydrochlorothiazide + Pravastatin</td>
</tr>
<tr>
<td>One or more uncomplicated atherosclerotic lesion in the carotid artery (intima media thickness 1.3–4.0 mm)</td>
<td>*All patients receive a controlled diet</td>
</tr>
</tbody>
</table>

SUMMARY

Hypertension is an important risk factor for the development of atherosclerosis and evidence that ACE inhibitors have beneficial effects in experimental models of atherosclerosis is accumulating. PHYLLIS will go some way to determine whether or not fosinopril,
with or without the addition of a lipid-lowering agent, can modify the progression of atherosclerosis in hypertensive, hypercholesterolemic patients. Currently, it is well established that ACE inhibitors are effective antihypertensive agents. Furthermore, they have been known to reduce cardiovascular mortality and morbidity in patients with congestive heart failure and after myocardial infarction. Given that hypertensives often have multiple risk factors, ACE inhibitors should be among the first-line therapies for the treatment of elevated blood pressure. In particular, fosinopril has been demonstrated to produce reliable blood pressure control and have beneficial effects on surrogate clinical end-points as well as benefits in experimental atherosclerosis. Due to its dual compensatory route of excretion, fosinopril is a particularly useful antihypertensive for use in elderly patients.

REFERENCES