Hypertension In The 1990s: A New Disease

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Background: Recent analyses of the cumulative results of the major treatment trials of mild-to-moderate hypertension have shown only a small benefit in the prevention of stroke and no benefit in the prevention of coronary heart disease.

Methods: A MEDLINE search for articles published from 1966 to 1991 was made using the key words “left ventricular hypertrophy,” “hypertension,” “insulin resistance,” and “cholesterol.” The bibliographies of these articles and articles previously abstracted in The Family Practice Newsletter (InforMed) and the author’s personal files were also sources of information.

Results and Conclusions: Newer pharmacologic agents for hypertension, the peripheral α-blockers, the calcium channel blockers, and angiotensin converting enzyme inhibitors, exert positive effects on left ventricular hypertrophy, serum lipids, and serum insulin and could be cardioprotective. These drugs offer the promise of being able to show cardiovascular benefits from the treatment of mild-to-moderate hypertension that were not realized in the earlier clinical trials.

Does the treatment of mild-to-moderate hypertension offer any proven benefits in the prevention of deaths from heart disease? Many physicians will be surprised to learn that the current answer is, “No.” The only benefit that has been proved from the treatment of mild-to-moderate hypertension is a small but significant reduction in both fatal and nonfatal strokes. Because hypertension is the second most frequent reason for visits to a family physician’s office, physicians need an adequate understanding of the current costs, risks, and benefits of its treatment.

This article reviews the data that have emerged since the major clinical hypertension trials and provides a framework for making appropriate treatment decisions for individual patients.

Lessons from the Major Clinical Trials

In 1989 Cutler, et al.2 and MacMahon, et al.3 reviewed the results of the available large-scale, controlled, clinical trials that reported the effects of drug treatment for mild-to-moderate hypertension. Among the aggregate 43,000 patients in the nine trials who were observed for an average of 5.6 years, mean diastolic blood pressure reduction was 5.8 mmHg, an 11 percent reduction in total mortality was observed.4-15

This benefit was largely attributable to a 38 percent reduction in fatal strokes and a 43 percent reduction in nonfatal strokes. Mortality from coronary heart disease was 8 percent lower in participants, but this reduction was not statistically significant, nor was the 6 percent lower incidence of nonfatal myocardial infarction. Figure 1 summarizes the results of these trials.

The absolute difference, however, between aggregate treated and control groups was only 51 fatal strokes, which implies that it is necessary to treat approximately 422 patients for 5 years to prevent one fatal stroke — a benefit that might be too small to persuade many patients to undergo treatment. A systematic analysis of this issue in the New Zealand literature16 frankly concluded that the treatment of mild hypertension for the prevention of stroke is not cost effective, even when based on diuretic agents; this report estimated that about 530 to 1375 patients would need to be treated for mild-to-moderate hypertension each year to prevent one stroke in those aged 35 to 64 years at a cost of $110,900 to $285,400 in 1982 US dollars.

Among the plausible explanations of the disappointing cardiovascular outcomes are that the trial sizes were too small or lacked power to detect small but significant effects on cardiovascular disease, treatment duration might not have been long enough, other risk factors were inadequately
controlled, crossover or contamination between treatment and control groups could have occurred, or the pharmacologic agents selected, primarily diuretics and $\beta$-blockers, were not the optimal drugs (because of metabolic side effects).

The trends in these data have been interpreted to suggest that the two major outcomes studied, stroke and coronary heart disease, represent different disease processes. Stroke appears to be the result of a more simple, pressure-related outcome with substantial reductions in risk achievable very soon after beginning treatment — an effect that is analogous to an overinflated balloon for which the risk of rupture diminishes markedly after release of only a small amount of pressure. In contrast, coronary heart disease appears to represent a biochemical process involving calcium, lipids, platelets, prostaglandins, insulin, fibrin, and smooth muscle metabolism, a process that is catalyzed in the presence of hypertension.

These findings suggest that a reconsideration of our previous bias in favor of treatment of mild-to-moderate hypertension is in order. Among the reasons not to treat the typical middle-aged hypertensive patient are the following:

1. The only proven benefit is stroke prevention, and stroke is simply not a very great risk in this age group, only about 1 per 1000.
2. The major risk of serious morbidity and mortality in this age group is cardiovascular disease (approximately 14 per 1000), which is
not greatly affected by treatment as far as we know.

3. Other risk factors have been recognized as having a more substantial role in cardiac morbidity and mortality and deserve greater attention than hypertension — for example, smoking, sedentary lifestyle, obesity, diet, and menopausal status.

4. New data clearly substantiate a major risk from the "overtreatment" of hypertension, known as the "J-curve phenomenon." Our treatment can actually harm patients if diastolic pressures less than 85 mmHg are achieved.

The treatment of moderate hypertension in the middle-aged patient is simply not a priority unless we can show that heart disease and its outcomes will be affected.

Hypertension and Heart Disease: New Prognostic Factors

New evidence has shown that several factors have an important prognostic significance for the outcome of mild-to-moderate hypertension. Chief among these are echocardiographically determined left ventricular hypertrophy, the effects of pharmacologic therapy on cholesterol and its subfractions and on insulin metabolism, and cardio-protection (the degree to which pharmacologic therapy can be effective in primary prevention of coronary heart disease).

Effect of Left Ventricular Hypertrophy

Left ventricular hypertrophy has emerged as the most important risk factor for adverse outcomes among hypertensive patients. The Framingham studies showed a highly significant correlation between electrocardiographic left ventricular hypertrophy and cardiac mortality. The sensitivity of electrocardiographic diagnosis of left ventricular hypertrophy, however, is poor. Echocardiographic left ventricular hypertrophy has been shown to be a much more sensitive marker for this condition and has a much better correlation with cardiovascular morbidity and mortality. Approximately 20 percent of the unselected ambulatory hypertensive population has left ventricular hypertrophy when studied by echocardiography compared with 1 to 4 percent by standard electrocardiography. In a study of 280 hypertensive patients, patients with normal left ventricular measurements on echocardiogram had the fewest adverse outcomes (no cardiac deaths, morbid events in 11 percent), whereas those with concentric hypertrophy had the most (death in 21 percent, morbid events in 31 percent). In a multivariate analysis from the same study, only age and left ventricular mass — but not sex, blood pressure, or serum cholesterol level — independently predicted all three outcome measures (Figure 2).

At least one study concluded that, at an average cost per M-mode echocardiogram of $160 and in populations with a 12 to 40 percent prevalence of left ventricular hypertrophy, echocardiography costs less than standard electrocardiography per instance of hypertrophy detected ($390 - $1013 versus $800 - $1829), yields better separation in predicted incidence of morbid events, and requires smaller case and control samples for hypothetical research studies. Regardless of whether one is persuaded to use echocardiography for screening and case detection of left ventricular hypertrophy, it would still appear logical to choose an agent that is capable of reversing left ventricular hypertrophy, if present, when one decides to treat mild-to-moderate hypertension pharmacologically. Among currently available antihypertensive medications, only diuretics and arteriolar dilators (hydralazine, trimazosin, and minoxidil) fail to reverse left ventricular hypertrophy. The failure of diuretics as monotherapy to lead to regression of left ventricular hypertrophy and the predominance of diuretics among therapeutic agents in the major hypertension trials could explain some of their disappointing results.

Effects of Antihypertensive Therapy on Lipid Metabolism

The Framingham data have shown that for every 1 percent change in serum cholesterol level, a 2 percent change in cardiovascular mortality in the same direction can be expected. Thiazide diuretics are commonly thought to be associated with an increase in serum cholesterol levels, but if this were truly the case, these diuretics would be contraindicated in the treatment of mild hypertension. In a careful review Moser argues persuasively that any increase in cholesterol with these agents is only short-term and that
the best available long-term data show no significant effect of diuretics on serum cholesterol level.

Noncardioselective β-blockers do not raise total serum cholesterol, but they do elevate very low density lipoprotein (VLDL) cholesterol and triglycerides by 30 to 40 percent, and they reduce high-density lipoprotein (HDL) cholesterol by 10 to 20 percent.28 Cardioselective β-blockers have similar but less pronounced effects. Only β-blockers with intrinsic sympathomimetic activity have a favorable effect on serum lipids — raising HDL cholesterol and leaving serum triglycerides unchanged.

Some of the newer antihypertensive medications have a consistently favorable effect on serum lipids. Verapamil can elevate serum HDL by up to 16 percent.29 Nifedipine has been reported to improve both HDL and triglycerides.30 The peripheral α-blockers, prazosin,31 terazosin,32 and doxazosin,33 significantly lower serum lipids. Doxazosin is a new agent in this class with particularly well-documented beneficial effects on lipids. The doxazosin study was an open, non-comparative, multicenter study involving 4027 patients during 10 weeks of treatment. Statistically significant differences between pre- and post-treatment lipid levels were found for total cholesterol (4.1 percent reduction), low-density lipoprotein (LDL) cholesterol (4.9 percent reduction), and triglycerides (8.4 percent reduction), HDL cholesterol (2.8 percent increase), and HDL-total cholesterol ratio (7.1 percent increase). When these changes and the change in blood pressure are entered into the Framingham equation34 for the calculation of coronary heart disease risk, the estimated total reduction in risk of coronary heart disease in the next 10 years is 20.4 percent — an effect of the same order of magnitude as shown by β-blockers given after a myocardial infarction.

Role of Insulin in Hypertension and "Syndrome X"

The most important new metabolic aspect of hypertension and its treatment to emerge in recent years is the role of insulin and insulin resistance.17,35,36 In 1969 Welborn, et al.37 observed that a certain proportion of patients with high blood pressure had higher than normal plasma
insulin concentrations in response to an oral glucose challenge. Since then several epidemiologic studies have confirmed a relation between insulin and cardiovascular morbidity and mortality. A 1979 study from Australia\textsuperscript{19} of 3390 adults showed that the men who were in the upper 20 percent of the insulin distribution 1 hour after a 50-g glucose load experienced a statistically significant increase in 6-year coronary heart disease incidence and in 12-year coronary heart disease mortality, as well as in 12-year cardiovascular disease mortality, independent of other cardiovascular disease risk factors, such as blood pressure and cholesterol.

A 1991 report from Finland\textsuperscript{39} extended this observation by showing a correlation of coronary heart disease with fasting plasma insulin levels. In this study, 909 noninsulin-dependent subjects and 1373 nondiabetic control subjects, aged 45 to 64 years, were stratified into quintiles based on their fasting plasma insulin levels. The age-adjusted prevalence of coronary heart disease for diabetic men was 48.2 percent for the lowest two quintiles, 54.8 percent for the middle two quintiles, and 65.7 percent for the highest quintile; in nondiabetic men, the prevalence of coronary heart disease for the lowest two quintiles was 28.1 percent, 33.7 percent for the middle two quintiles, and 43.3 percent for the highest quintile. The rates for women were similar but slightly lower (Figure 3).

Current evidence also suggests that a defect in insulin metabolism clearly precedes hypertension rather than results from it.\textsuperscript{40} A prospective study compared insulin sensitivity, plasma insulin and glucose, and serum lipoproteins in two normotensive groups: 70 offspring of persons with essential hypertension and 78 control subjects from normotensive families, matched for age and body mass index. Compared with control subjects, study subjects with hypertensive parents had statistically significant elevations in fasting plasma insulin, total triglycerides, LDL cholesterol, and the ratio of total to HDL cholesterol; they also had significantly lower insulin sensitivity and higher post-glucose-load plasma insulin levels.

Insulin resistance is also associated with an increased VLDL-triglyceride secretion rate and plasma triglyceridemia. Compared with healthy
subjects, hypertensive subjects without coronary artery disease, normotensive patients with coronary disease, and hypertensive patients with coronary artery disease, all have progressively and significantly greater levels of serum triglycerides. The importance of hypertriglyceridemia and concomitant low HDL cholesterol as a primary risk factor for coronary heart disease is being newly emphasized in a recent update from the Framingham study.

The hypertension-associated abnormalities of insulin metabolism do not resolve with treatment of hypertension, even if the blood pressure is well controlled. Under experimental conditions, hypertensive and control subjects infused with somatostatin, insulin, and glucose achieved similar steady-state plasma insulin levels, but both groups of the hypertensive subjects (both untreated and treated) had significantly higher steady-state plasma glucose concentrations, indicating resistance to insulin-stimulated glucose uptake (Figure 4). Many agents used in the treatment of hypertension aggravate this defect in insulin metabolism. Thiazide therapy is associated with a 16 percent decrease in insulin sensitivity. β-Blockers have been associated with a 20 percent decrease in insulin-sensitivity manifested by decreases in glucose uptake and increases in fasting plasma insulin, glucose, glycosylated hemoglobin, and VLDL and LDL-triglyceride concentrations.

There are now two classes of drugs available that improve insulin metabolism. Pollare, et al. have shown that the angiotensin converting enzyme (ACE) inhibitor captopril leads to an 11 percent increase in insulin sensitivity, as measured with the euglycemic insulin clamp technique, and an even greater increase (18 percent) in the insulin sensitivity index, which corrects for the prevailing insulin concentration. The peripheral α-blockers have also been shown to enhance insulin sensitivity. Doxazosin, for example, after 26 weeks of treatment led to a 5 percent lowering

![Figure 4: The effect of insulin metabolism on cardiovascular mortality in untreated and treated hypertensives.](image-url)
of serum glucose and a 17 percent lowering of fasting serum insulin levels in a group of patients with mild hypertension.

The calcium channel blocking agents appear to have either no effect or a mild beneficial effect on insulin and lipid metabolism.\textsuperscript{40,43,51}

The various metabolic disturbances in lipids and insulin metabolism described above tend to occur together in the hypertensive patient. To describe this phenomenon, Reaven\textsuperscript{52} coined the term "syndrome X" to indicate a state of insulin resistance, glucose intolerance, hyperinsulinemia, increased VLDL triglyceride, decreased HDL cholesterol, obesity, and hypertension; these hypertensive patients are currently recognized as being at the greatest risk for adverse cardiovascular events.

**Cardioprotection**

The concept of cardioprotection developed as a result of the trials of \(\beta\)-blockade in the setting of acute myocardial infarction. The results of 25 randomized trials involving more than 23,000 patients showed that long-term \(\beta\)-blocker therapy after a myocardial infarction led to a 22 percent reduction in the risk of death and a 27 percent reduction in nonfatal reinfarction.\textsuperscript{53} This finding led to an investigation of whether \(\beta\)-blockers might have any similar benefit, independent of their blood-pressure-lowering effect, in the primary prevention of infarction and sudden death among patients whose only risk factor is hypertension.

In a 1988 report published in \textit{JAMA}, the MAPHY Study,\textsuperscript{54} the authors suggested that exactly this result could be achieved. In a population of 3234 patients randomized to treatment with either metoprolol or a diuretic, a difference in total mortality of 48 percent was found in favor of patients randomized to metoprolol.

In 1989, however, several reviews appeared in \textit{Hypertension}\textsuperscript{55,56} that found substantial flaws in the MAPHY report. Particularly noteworthy is that the metoprolol results did not hold true for the patients from the same study treated with atenolol. The authors of these latter reports concluded firmly that \(\beta\)-blockers have thus far failed to live up to their cardioprotective promise.

This issue is still not resolved. In 1991 the authors of the MAPHY report published an update extending their follow-up of this cohort of patients\textsuperscript{57} and were able to show a persistent 24 percent reduction in the risk of coronary events. Presently, the only reasonable conclusion to draw from these data is that, among \(\beta\)-blockers, metoprolol could have a cardioprotective effect in the treatment of hypertension; it is clearly unsafe to generalize this conclusion to other \(\beta\)-blockers.

Despite some initial promising reports, calcium channel blockers are not cardioprotective in the setting of acute myocardial infarction.\textsuperscript{58} Newer data, however, from the International Nifedipine Trial on Antiatherosclerotic Therapy (INTACT)\textsuperscript{59} suggest that nifedipine might be cardioprotective in primary prevention. This trial was conducted on 425 patients with mild coronary artery disease on initial arteriography, who were randomized to treatment with nifedipine (80 mg/d) or placebo; 3 years later 82 percent of the subjects underwent repeat arteriography with computer-assisted analysis of the results. The authors found no differences between the treatment group and the placebo group in either the progression or regression of established lesions, but they found that the number of new arteriosclerotic lesions was reduced by 28 percent.

An mentioned above for the peripheral \(\alpha\)-blocker doxazosin, the 20.4 percent reduction in predicted 10-year mortality that resulted from its favorable effects on lipids is tantamount to a cardioprotective effect.

**Clinical Treatment Decisions**

In view of the coronary artery disease paradox,\textsuperscript{16} that is, the apparently successful sustained reduction of blood pressure without measurable cardiovascular benefit, in the context of the above data, the traditional stepped care approach is being succeeded by a less interventionistic, highly individualized risk-benefit analysis in making treatment decisions. Representative of the more modern approach is this recommendation from Flack and Sowers:

\begin{quote}
Choices between different pharmacologic regimens in most instances will be made on criteria \textit{other than} blood-pressure-lowering efficacy, since the most commonly used antihypertensive drug classes, by and large, all lower blood pressure equally. Other criteria—such as cost, tolerability, coexisting medical conditions, and
\end{quote}

Hypertension in the 1990s 249
the potential protection afforded against CHD [coronary heart disease] — form the basis for selecting antihypertensive drug therapy. Abnormalities in lipoprotein and carbohydrate metabolism are well established risk factors for CHD. A prudent approach to treating hypertensive patients is therefore one that optimizes the potential for coronary risk reduction during blood pressure normalization. This approach appears to be one that does the following: (a) maximizes life-style interventions like weight loss and appropriate physical activity; (b) if blood pressure control is not achieved with these therapies, adds antihypertensive drugs that improve, or at least do not adversely influence, other aspects of the CHD risk profile, such as blood lipids and insulin resistance; and (c) manages all other identified cardiovascular risk factors. For those patients meeting one of these criteria for undertaking pharmacologic therapy, the modern physician should consider the following major clinical variables:

1. Ability to lower blood pressure
2. Effects on left ventricular hypertrophy
3. Effects on total cholesterol and LDL
4. Effects on HDL cholesterol
5. Effects on triglycerides
6. Effects on insulin metabolism
7. Cardioprotection

When a drug is indicated, the prescribing decision can be simplified by referring to a grid reflecting the data discussed above (Table 1).

### Table 1. Selection of an Antihypertensive Agent.

<table>
<thead>
<tr>
<th>Clinical Effect</th>
<th>Pharmacologic Class</th>
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<tbody>
<tr>
<td>Reduces blood pressure</td>
<td>Diuretics β-Blockers</td>
</tr>
<tr>
<td>Regresses left ventricular hypertrophy</td>
<td>Calcium Blockers Inhibitors</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>α-Blockers</td>
</tr>
<tr>
<td>High-density lipoprotein</td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
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<tr>
<td>Cardioprotective</td>
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</tbody>
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α-Blockers have a mixed effect on cholesterol fraction: low-density lipoprotein (LDL) is not affected, but very low density lipoprotein (VLDL), low-density lipoprotein triglycerides, and high-density lipoprotein (HDL) are adversely affected.

Among calcium channel blockers only verapamil and nifedipine have been clearly shown to increase HDL significantly.

Calcium channel blockers are generally thought to have no effect on insulin metabolism, but some data to the contrary exist for verapamil and nifedipine.

**Diuretics elevate cholesterol in the short-term, but during the long-term they either have no effect or slightly lower the cholesterol.

*β-Blockers have a mixed effect on cholesterol fraction: low-density lipoprotein (LDL) is not affected, but very low density lipoprotein (VLDL), low-density lipoprotein triglycerides, and high-density lipoprotein (HDL) are adversely affected.

Among calcium channel blockers only verapamil and nifedipine have been clearly shown to increase HDL significantly.

Calcium channel blockers are generally thought to have no effect on insulin metabolism, but some data to the contrary exist for verapamil and nifedipine.

**Diuretics are clearly not cardioprotective; the MRRT trial suggests that they could be a specific risk factor for adverse cardiac outcomes in the context of hypertensives with abnormal baseline electrocardiograms (ECG).

Among β-blockers only metoprolol has any reasonable data to suggest that it could be cardioprotective in primary prevention.

**The best evidence in favor of a cardioprotective effect for calcium channel blockers is the INTACT study for nifedipine; this finding needs to be confirmed before nifedipine is clinically implemented for this rationale.

Peripheral α-blockers are considered cardioprotective because of the magnitude of their favorable effect on serum lipids with the estimated 20 percent reduction in 10-year cardiovascular mortality.
This analysis supports peripheral α-blockers as first-line monotherapy for mild-to-moderate hypertension. This conclusion derives from their combination of enhancing insulin sensitivity and enhancing the lipid profile while achieving reductions in blood pressure equal to that of other agents in a once-daily dose at a reasonable cost. In different situations other drugs would be preferred first-line alternatives:

**Angina**
Those calcium channel blockers that have been approved as antianginal medications are the logical first choice in the treatment of hypertensive patients who have documented coronary artery disease and symptomatic angina.

**Diabetes**
The ACE inhibitors are the logical first choice in diabetic patients because of both their insulin-enhancing effects and their proven renal-protective effects.

**Congestive Heart Failure**
ACE inhibitors should be considered drugs of choice because they (captopril and enalapril) are the only drugs that have been shown to improve significantly the mortality associated with chronic congestive heart failure.

**Post-Myocardial Infarction**
The best role for β-blockers in hypertension would appear to be in the patient who remains hypertensive after a myocardial infarction.

Even in these groups of patients, the peripheral α-blockers constitute an excellent choice as a second-line agent, where necessary, because of their favorable metabolic effects. The continued role of thiazide diuretics in the treatment of mild-to-moderate hypertension is problematic. Given the failure of diuretics to reverse left ventricular hypertrophy, their antagonism of insulin metabolism, and the failure of the major clinical trials that used diuretics to affect heart disease favorably, it is difficult to recommend them except for frankly congestive or edematous states.

**Comment**
The analysis here raises as many questions as it attempts to answer. Among the specific issues that we should address as we read the future medical literature are the following:

1. Will selection of patients for pharmacotherapy on the basis of echocardiographically determined left ventricular hypertrophy lead to improved clinical outcomes?
2. Will future data confirm the INTACT study and settle the issue of whether calcium-channel blockers are cardioprotective?
3. Will longer term trials of peripheral α-blockers result in the predicted 20 percent reduction in cardiovascular events?
4. Will a properly designed prospective trial of β-blockers in primary prevention of coronary heart disease confirm the results of the MAPHY trial?
5. Will ACE inhibitors be shown to have a cardioprotective effect in primary prevention of congestive heart failure?
6. Do calcium channel blockers and peripheral α-blockers have a renal-sparing effect in diabetic patients similar to that of the ACE inhibitors?
7. Would trials in the elderly, such as the SHEP trial and the STOP-Hypertension trial, have achieved even more favorable results had therapeutic agents with more favorable metabolic effects been used?
8. Would patients with severe hypertension, even though they have clearly benefitted from existing therapeutic agents, benefit even more if they were treated with agents with more favorable metabolic profiles, such as the α-blockers, calcium channel blockers, and ACE inhibitors?
9. Finally, would the major clinical trials of the treatment of mild-to-moderate hypertension, if they were repeated with the newer agents, lead to demonstrable benefits in the prevention of adverse cardiovascular outcomes, as well as in the prevention of stroke?

It is clear that all physicians who treat hypertension would benefit from a repetition of the major clinical trials with our newer agents. The results might very well fulfill our hopes of improved cardiovascular outcomes. Unfortunately, it is unlikely that the resources necessary to mount these efforts will be made available. New evidence in hypertension will more likely develop slowly and
in a piecemeal fashion. In the future, to practice good medicine and to provide the best care for our patients, we in primary care must accept the challenge of keeping up with this rapidly changing body of knowledge. In the 1980s, while we were not looking, hypertension became an entirely different disease. The task of the 1990s is to redirect our therapeutic efforts to anticipate the clinical answers that should have solid supporting data by the year 2000.

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