Recommendations of the Adult Treatment Panel of the National Cholesterol Education Program
Implications for the Management of Hypertension

HYPERTENSION is recognized as a major cardiovascular risk factor. Multiple clinical trials have shown that the treatment of high blood pressure reduces the incidence of stroke, congestive heart failure, and perhaps, renal insufficiency. However, these trials failed to demonstrate a consistent impact of antihypertensive therapy on coronary heart disease events. Although the exact reasons for this observation are not clear, several explanations have been proposed. One possibility is that hypertension and atherosclerosis are not causally related despite suggestions from epidemiological data. A second explanation is that treatment of hypertension in patients with preexisting coronary artery disease may precipitate coronary ischemia in some patients in whom coronary perfusion pressure is greatly reduced. A third and popular explanation is that the drugs that were employed in these trials (principally diuretics and β-blockers) induce metabolic side effects, including serum lipid abnormalities, glucose intolerance, and hypokalemia, that consequently may increase the overall coronary heart disease risk of the subjects under treatment. Thus, a tradeoff between lowering one risk factor (hypertension) and increasing another (lipid or glucose abnormalities) may negate the beneficial effects of antihypertensive therapy on coronary risk. The latter postulate has led physicians to reevaluate the conventional approach to the treatment of hypertension and to search for alternative forms of therapy.

With the recent data on the causal relationship between serum cholesterol and coronary heart disease, much attention has shifted to the treatment of dyslipidemia. A number of milestone trials (Lipid Research Clinics Coronary Primary Prevention Trial, Helsinki Heart Study, Coronary Drug Project) demonstrate clearly that the lowering of serum cholesterol reduces coronary heart disease events. With the appreciation that hypertensive subjects frequently have hypercholesterolemia and the reports that certain antihypertensive agents (e.g., diuretics and β-blockers) may induce adverse serum lipid changes, there has been much emphasis on selecting antihypertensive drugs that have no adverse effects on serum lipids. The proponents of this practice frequently cite the epidemiological data on cholesterol and coronary heart disease as well as the cardioprotective effects of lowering cholesterol. However, there is much debate on the duration of the serum lipid abnormality induced by these drugs (e.g., diuretics). Furthermore, the magnitude of the diuretic-induced hypercholesterolemia is usually modest (7–10% increase). The proponents for conventional antihypertensive therapy argue that there are insufficient data on the cardioprotective effect of alternative and newer forms of antihypertensive therapy (i.e., converting enzyme inhibitors, α1-antagonists, and calcium channel blockers) to warrant a change from the conventional approach. Since multicenter placebo-controlled trials to study the impact of these newer forms of antihypertensive therapy on coronary heart disease are not likely to be forthcoming, physicians are left without definitive data on which to base their selection of antihypertensive drugs aiming to decrease coronary heart disease. The debate on this subject continues.

Another much discussed issue is the cost of drug therapy and the effects of such therapy on compliance and on the quality of life. Although most physicians
acknowledge that certain drugs (e.g., diuretics, β-blockers, and centrally acting drugs) have undesirable effects on the patient's quality of life, cost and compliance appear to be overriding issues for the average practitioner in the decision to use these drugs. This is a questionable rationale for the selection of diuretic therapy. In my opinion, the argument in favor of such a choice based on compliance and cost breaks down if the drug induces metabolic side effects that require pharmacological correction (i.e., potassium replacement for hypokalemia, oral hypoglycemic or insulin therapy for worsening diabetes, uricosuric drugs for hyperuricemia, and lipid-lowering drugs for increased serum cholesterol induced by antihypertensive drugs).

The recommendations of the Adult Treatment Panel of the National Cholesterol Education Program on the treatment of hypercholesterolemia adds fuel to this controversy. The report recommends that a patient with borderline high serum cholesterol (i.e., serum total cholesterol concentration of 200–239 mg/dl) without coronary artery disease but with two other risk factors undergo lipoprotein analysis. If the low density lipoprotein (LDL) cholesterol level is greater than 160 mg/dl (high risk), lipid-lowering intervention is indicated. A patient whose LDL cholesterol is in the borderline high risk range (i.e., 130–159 mg/dl) and who has two other risk factors should also be treated. *Treatment should always start with nonpharmacological therapy.* The report defines risk factors as hypertension, diabetes, cigarette smoking, and left ventricular hypertrophy. It should be noted that male gender is also considered a risk factor. Since the average hypertensive patient is a middle-aged man whose serum cholesterol is in the borderline high risk category, recommendations of the Adult Treatment Panel will have a significant impact on the management of a large population of patients.

To illustrate this issue, let us consider a middle-aged man with mild to moderate hypertension, a serum cholesterol level of 220 mg/dl, and an LDL cholesterol level of 140 mg/dl. In addition to antihypertensive therapy, this patient will require treatment for his elevated serum cholesterol. The first and fundamental step of lipid-lowering treatment is nonpharmacological therapy. This is appropriate since lipid-lowering drugs are far from being free of side effects. Drugs of first choice, such as nicotinic acid and bile acid resins, are difficult to tolerate. With the exception of nicotinic acid, lipid-lowering drugs are expensive. It should be noted that the choice of antihypertensive agent may enhance or jeopardize the potential success of dietary therapy in lowering the serum cholesterol in such a patient. In other words, agents such as diuretics, through their adverse effect on serum lipid levels, may negate or attenuate the effect of a low fat diet on serum cholesterol levels. Under these circumstances, a lipid-lowering drug may then be administered. Hence, the cost of treating this mildly to moderately hypertensive patient with a borderline high risk cholesterol level will escalate. Certainly, compliance may also become a problem.

The effect of antihypertensive agents on serum lipids may also influence the management of a patient with normal serum cholesterol levels. Consider a man with mild to moderate hypertension, a serum cholesterol level of 195 mg/dl, and an LDL cholesterol level of 125 mg/dl. A 10% increase in serum and LDL cholesterol induced by an antihypertensive agent may shift this patient into the borderline high risk category and consequently require lipid-lowering therapy. If physicians follow the recommendations of the Adult Treatment Panel, and I hope they will, the impact of the recommendations on the selection of antihypertensive drugs becomes an extremely relevant subject.

The practice of preventive cardiology is based on the premise that the benefits derived from the treatment of cardiovascular risk factor(s) outweigh the adverse effects of the treatment. There is already much debate on the high monetary cost of saving one life through the administration of lipid-lowering drugs. Fortunately, many physicians as well as the general public believe that one simply cannot place a price on saving a life. Nevertheless, I for one would like to know that my patients are deriving benefits from the therapy that I prescribe. The untoward side effects and the costs of medicine are high prices to pay. However, these prices are worthwhile if one can be assured of achieving long-term benefits. In the context of hypertension therapy, it is clearly preferable, in my opinion, to use agents that do not affect serum lipids or other risk factors (e.g., angiotensin
converting enzyme inhibitors, \( \alpha_1 \)-antagonists, or calcium channel blockers) in order to avoid the potential adverse influence on coronary heart disease risk and the additional cost of lipid-lowering therapy.

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