Clinical Conference

Optimizing Cardiovascular Risk Reduction During Antihypertensive Therapy

Principal Discussant
Myron H. Weinberger

Hypertension Research Center, Indiana University School of Medicine, Indianapolis, Indiana

Over the past decade, pharmacological treatment of elevated blood pressure has evolved from empiricism to a more individualized approach based on patient characteristics and an expanding understanding of the impact of specific agents on the pathophysiology of hypertension and, more importantly, cardiovascular disease. Although blood pressure elevation has been shown to be a powerful risk factor for myocardial infarction, stroke, congestive heart failure, and renal failure, as well as several other forms of cardiovascular disease, epidemiological evidence has supported the additive impact of other risk factors as well.1 The presence of cigarette smoking, left ventricular hypertrophy, dyslipidemia, and hyperglycemia, as well as increases in uric acid and serum fibrinogen levels, enhance the effects of elevated blood pressure on all forms of cardiovascular disease. The increasing understanding of the hemodynamic and metabolic effects of specific antihypertensive agents, and the recognition that not all effective blood pressure-lowering strategies have been demonstrated to have uniform or consistent benefit in reducing all forms of cardiovascular disease associated with hypertension, has forced a critical reevaluation of the effects of specific antihypertensive drugs.

Current Understanding of Cardiovascular Risk Factors

The overwhelming majority of evidence identifying and quantifying risk factors for various forms of cardiovascular disease has come from several epidemiological studies. Although these observations are extremely important in identifying such factors, it has been difficult to evaluate the contribution of a single component in these multifactorial disorders. Interventional studies provide only limited information because of the difficulty in assessing the effects of single factors, particularly in high risk individuals. This problem is compounded by the ethical constraints against placebo or less effective treatment comparisons in individuals with manifest disease and the use of fatal end points.

The initial trials of antihypertensive therapy conducted by the Veterans' Administration Cooperative Study Group were the first to show that active, drug-induced reduction of elevated blood pressure using a multiple drug approach was associated with a significant decrease in cardiovascular morbidity and mortality compared with a placebo-treated group where no blood pressure decline was seen. These observations were initially reported in severe hypertensive patients (diastolic blood pressure 115–129 mm Hg)2 and later extended to those with less striking hypertension (diastolic blood pressure 90–114 mm Hg).3 This led to the traditional “stepped-care” treatment algorithm. It is important to note that, although the Veterans' Administration studies demonstrated a reduction in overall morbidity and mortality, no such decrease was seen in the incidence of coronary artery disease. The striking reduction in overall cardiovascular morbidity and mortality resulting from several trials using this algorithm has made the use of placebo-controlled, parallel-group trials difficult to justify on an ethical basis. In 1980, two placebo-controlled trials raised concerns about a potential adverse effect of diuretic treatment on coronary disease.4 5 The large Multiple Risk Factor Intervention Trial (MRFIT), which focused on three risk factors (smoking, cholesterol, and blood pressure), observed an increased rate of sudden death among diuretic-treated hypertensive men who entered the study with electrocardiographic abnormalities.6 The Hypertension Detection and Follow-up Program (HDFP) demonstrated that stepped-care, which lowered diastolic pressure about 5 mm Hg more than the comparison “referred-care” group, resulted in an overall 45% reduction in stroke mortality but only a 25% reduction in cardiovascular deaths.7 Furthermore, a retrospective analysis of the HDFP data demonstrated the same increase in sud-
Dyslipidemia and Atherosclerosis

Epidemiological studies linking elevated levels of blood cholesterol to an increased risk of death from coronary artery disease have stimulated an enormous body of work that has provided a clearer understanding of the atherogenic process contributing not only to coronary artery disease but cerebrovascular, peripheral vascular, and renal disease as well. Although the original observations identified total serum cholesterol as the factor related to myocardial infarction, we now know that the lipoproteins, which are responsible for cholesterol transport, are the major determinants of atherogenesis. The major lipoprotein is the low density fraction (LDL), which is removed from plasma by binding to receptors at the cell surface. However, high levels of cholesterol suppress LDL receptors, which leads to an increase in LDL levels in plasma. LDL can also be taken up by macrophages, which in turn form foam cells and initiate development of an atheromatous plaque. The high density lipoprotein (HDL) is the antiatherogenic lipid component and is increased by exercise, alcohol, and estrogen, and thus is higher in women than in men. The strongest relations between lipids and heart attacks have been the inverse link with plasma HDL levels.

Several factors augment the atherogenic effect of circulating lipids. Elevation of blood pressure is a potent enhancer of vascular lesions along with diabetes mellitus and cigarette smoking. As previously noted, although the mechanical complications of hypertension can be shown to be reduced by blood pressure reduction, convincing evidence of a similar beneficial effect on atherosclerotic complications is less extensive. In experimental animal models of atherosclerosis such as the Watanabe heritable hyperlipidemic rabbit, elevation of blood pressure by renal artery clipping increased the extent of aortic atherosclerosis twofold to fourfold. Similar observations have been reported for cholesterol-fed animals in which hypertension has been induced. Thus, there is abundant evidence linking these experimental observations to the increased incidence of atherosclerosis in hypertensive humans. In normotensive animals treated with diuretics or B-blockers, decreases in atherogenesis have been seen, presumably attributable to the decrease in heart rate or blood pressure.

We now know that dyslipidemia is more frequent in hypertensive than normotensive individuals. While recognizing the acceleration of atherosclerosis when hypertension is present and the large number of atherosclerotic complications of hypertension such as coronary artery disease and myocardial infarction, stroke, aneurysm, and renal or peripheral vascular disease, it is important to consider the possibility that specific approaches may limit the progression of atherosclerosis or even induce regression of existent atheromatous lesions. The impact of specific antihypertensive agents on lipids and atherosclerosis will be subsequently discussed, but a few comments regarding the reversibility of atherosclerotic lesions may be worthwhile. A recent screening study of over 361,000 American men disclosed a linear relation between total serum cholesterol and coronary disease mortality over a 6-year follow-up period, which began to increase significantly at levels of cholesterol above 181 mg/dl. In high risk subjects, reduction of elevated cholesterol levels has been repeatedly demonstrated to reduce the incidence of coronary events. The Lipid Research Center Coronary Primary Prevention Trial demonstrated a 2% reduction in coronary events for each 1% reduction in total cholesterol over an average of 7.4 years. A subsequent report from this same study demonstrated a 5.5% reduction in coronary events for every 1 mg/dl increase in HDL cholesterol. This was confirmed in the Helsinki heart study as well. Two recent studies have demonstrated...
regression of coronary atherosclerosis in patients with known coronary artery disease after diet and drug-induced reduction in cholesterol and LDL levels.\textsuperscript{22,23}

**Cigarette Smoking**

Cigarette smoking also enhances atherosclerosis and contributes to cardiovascular disease. Treated hypertensive patients who smoke have a twofold-to-threefold higher mortality rate than nonsmoking hypertensive patients.\textsuperscript{24} Although the mechanisms responsible for these relations are less clear, several factors may be involved. Nicotine may have a direct effect on the coronary circulation or on blood vessels in general in addition to producing hypoxia by the accumulation of carbon monoxide. Hypertensive patients who smoke were observed to have a greater degree of dyslipidemia than nonsmokers in another epidemiological study.\textsuperscript{25} Further, smoking increases fibrinogen levels, another known risk factor for cardiovascular disease.\textsuperscript{26} Some studies have suggested an interaction of cigarette smoking with some antihypertensive agents, reducing their efficacy.\textsuperscript{27}

**Obesity**

Although obesity has generally been found to be associated with an increased cardiovascular disease risk, several studies have indicated that this risk is attributable to elevated blood pressure, dyslipidemia, or diabetes often observed in obese individuals. Thus, when corrections are made for the effects of elevated blood pressure, lipids, and glucose in obese subjects, no independent contribution of body weight was observed. New observations, however, suggest a common link for several of these abnormalities. Obesity is associated with dyslipidemia. Men with predominant upper body obesity, as opposed to lower body ponderosity, have increased levels of atherogenic lipids (triglycerides, cholesterol, and LDL) and decreased HDL.\textsuperscript{28} When obese men lost weight by diet or exercise, similar decreases in triglycerides and increases in HDL were seen.\textsuperscript{29}

Total serum cholesterol levels were found to correlate with total testosterone levels in men as well as a correlation between total estradiol and cholesterol or high density lipoproteins.\textsuperscript{30} In obese women, less consistent changes in lipoproteins have been observed. With diet-induced weight loss, a significant reduction in triglycerides and LDL and an increase in HDL was seen without a correlation with plasma testosterone levels.\textsuperscript{31} Part of the explanation for differences between obese men and women in the responses of lipids to weight loss may result from gender differences in fat distribution.\textsuperscript{32} Estrogens increase HDL levels\textsuperscript{33} and androgens reduce them.\textsuperscript{34,35} These sex hormone-related changes in lipids may account for the relative protection against coronary artery disease seen in premenopausal women and the reversal of this protection along with increases in LDL and decreases in HDL observed after menopause.\textsuperscript{36}

**Hyperinsulinemia and Insulin Resistance**

Obesity is also associated with insulin resistance, hyperinsulinemia, and often frank diabetes mellitus. The hyperinsulinemia is more striking in those with upper body obesity as opposed to lower body obesity and may be enhanced by reduced hepatic extraction of insulin, which was found to be inversely related to plasma testosterone levels in obese women.\textsuperscript{37} Several studies have now reported hyperinsulinemia or insulin resistance in nonobese hypertensive patients.\textsuperscript{38-42} Recent studies in obese adolescents indicate that exercise and weight loss results in a decrease in both insulin levels and blood pressure.\textsuperscript{43} Further consideration of the effects of antihypertensive agents on insulin and glucose metabolism will follow in the discussion of the specific drugs.

**Left Ventricular Hypertrophy**

Left ventricular hypertrophy has been implicated as an important independent risk factor for cardiovascular disease.\textsuperscript{44} A common observation in hypertensive patients, left ventricular hypertrophy is a major contributor to congestive heart failure. As the myocardium becomes hypertrophic, demand for cellular oxygen supply often exceeds available coronary flow.\textsuperscript{45} The latter is often reduced because of coronary artery disease, and thus the mismatch between supply and demand may contribute to myocardial ischemia and infarction. Left ventricular dysfunction is not uncommon in the hypertrophied hypertensive heart. Moreover, the damaged or hypertrophied myocardium is more susceptible to cardiac arrhythmias. This latter observation may explain the increased risk of sudden death in recent clinical trials in hypertensive men treated with diuretics who had evidence of electrocardiographic abnormalities, most often those of left ventricular enlargement or strain.\textsuperscript{46} The stimuli for ventricular hypertrophy include increases in pressure or extracellular blood volume as well as at least two vasoactive agents, catecholamines and angiotensin II. Thus, it is not surprising, as will be detailed shortly, that not all antihypertensive agents have equal impact on the hypertrophied heart. Rather, their relative effects on pressure, volume, the renin-angiotensin and sympathetic nervous systems, and the myocardial contractile machinery determine whether the hypertrophied myocardium demonstrates regression along with decreases in blood pressure.

**Other Risk Factors: Uric Acid and Fibrinogen**

Recent evidence from the Framingham study has suggested an independent link between uric acid levels and blood fibrinogen content and cardiovascular disease.\textsuperscript{47} A clear rationale for a direct causal relation between uric acid and cardiovascular disease is not yet available. There are, as yet, no reported intervention studies to confirm a cause-and-effect situation. Many experts have suggested that uric acid elevations may be a marker for the presence of renal disease, perhaps subsequent to arteriolar nephroscler-
Diuretics and Hypokalemia

Diuretics lower blood pressure initially by reducing extracellular fluid volume, although long-term effects include attenuation of the dose–response relations to pressor agents. Diuretics have a variety of consequences that may adversely impact on cardiovascular disease risk.49 Consequent to reduction of extracellular fluid volume, compensatory activation of the renin-angiotensin-aldosterone and sympathetic nervous systems may limit the blood pressure reduction. Activation of the renin-angiotensin-aldosterone cascade with diuretic therapy leads to potassium secretion and hypokalemia by an aldosterone-dependent, receptor-mediated exchange for sodium and hydrogen ions in the collecting duct of the kidney. A parallel loss of potassium is usually observed with diuretic therapy. With long-term diuretic treatment, serum potassium levels may underestimate total body potassium deficits.50 Diuretic-induced potassium loss is influenced by several factors, including the magnitude of the renin-aldosterone response to volume depletion, dietary sodium and potassium intake, renal function, type and dose of diuretic,51 and administration of agents influencing potassium balance (potassium supplements, potassium-sparing drugs), aldosterone (spironolactone, angiotensin converting enzyme inhibitors), or renal function (nonsteroidal anti-inflammatory agents). In general, the potassium-losing threshold of thiazide-type diuretics is the same as the threshold for blood pressure response when used as monotherapy (approximately 25 mg). Loop diuretics, by virtue of their briefer duration of action, are less likely to cause hypokalemia and other metabolic effects if given once daily than are longer-acting agents. However, antihypertensive effects require administration of loop diuretics two or more times a day. In this circumstance, similar metabolic changes are seen. The longer-acting diuretics such as metolazone and chlorthalidone produce greater potassium loss at an equivalent blood pressure–lowering dose in comparison to thiazides because of the prolonged sodium-hydrogen ion for potassium exchange. However, a recent reformulation of metolazone (Mykrox, Fisons Corporation, Rochester, N.Y.) provided enhanced bioavailability of the agent and an antihypertensive potency at 0.5 mg/day in contrast to substantially higher doses required for blood pressure reduction with Zaroxolyn (Fisons). At this dose, minimal hypokalemia was observed.52 Indapamide has also been reported not to cause hypokalemia at doses of 2.5 mg/day or less in one study,53 but in two other studies, a slight but statistically significant decrease was seen at the same dose.54,55 Administration of copious amounts of supplemental potassium (60–120 meq/day) or potassium-sparing agents can prevent diuretic-induced hypokalemia. However, the expense and relative unpalatability of the former and the potential side effects and variable efficacy of the latter often make these approaches unsatisfactory. The angiotensin converting enzyme inhibitors, by interrupting the compensatory activation of the renin-angiotensin-aldosterone system, have been shown to attenuate diuretic-induced hypokalemia and enhance the antihypertensive efficacy of these agents.56,57 Similarly, diuretic-induced hyperuricemia, which may be an independent cardiovascular disease risk factor,46,58 has been shown to be influ-
enced by angiotensin II and can thus be prevented by combining diuretics with angiotensin converting enzyme inhibitors. In addition, the combination enables blood pressure control with lower doses of each agent than are required when they are administered as monotherapy. A discussion of the relations between diuretic-induced hypokalemia and hypomagnesemia, and cardiac arrhythmias and sudden death can be found in detail in a recent review.

**Insulin Resistance and Hyperglycemia**

Diabetes and hypertension concomitantly exist with a greater frequency than might be predicted by the occurrence of each disorder independently. In addition, recent evidence suggests that hyperinsulinemia and resistance to the glucose-disposing effects of insulin may be common characteristics of essential hypertensive patients as well as those with noninsulin-dependent diabetes mellitus. Although considerable debate exists regarding the causal relations between these abnormalities of carbohydrate metabolism and hypertension and cardiovascular disease, there is no question about an association between them. Although these abnormalities have been observed in untreated hypertensive subjects, it is particularly important to consider the known effects of antihypertensive therapy on insulin and carbohydrate metabolism.

Thiazide diuretics consistently induce hyperinsulinemia, insulin resistance, or hyperglycemia. Several mechanisms have been suggested for this phenomenon. Diuretic-induced hypokalemia has been shown to decrease carbohydrate tolerance in addition to decreasing insulin sensitivity of peripheral tissues. Diuretics also may have a direct effect on pancreatic insulin secretion or its metabolic clearance. Recent studies, using the sophisticated euglycemia "clamp" techniques, have demonstrated differential effects of several antihypertensive agents on insulin sensitivity. Blocker-β-adrenergic receptor blocker prazosin and the angiotensin converting enzyme inhibitor captopril have both been shown to improve insulin sensitivity, reduce hyperinsulinemia and hyperglycemia, and improve the lipid profile of essential hypertensive patients. The peripheral α-adrenergic receptor blocker prazosin and the angiotensin converting enzyme inhibitor captopril have both been shown to improve insulin sensitivity, reduce hyperinsulinemia and hyperglycemia, and improve the lipid profile of essential hypertensive patients. This may explain the prevention of diuretic-induced hyperglycemia reported when captopril was combined with hydrochlorothiazide. Diltiazem has been reported to have no effect on insulin sensitivity, whereas verapamil improved insulin sensitivity in patients with renal failure. A variety of factors may be responsible for these diverse effects of antihypertensive agents on insulin and carbohydrate metabolism including alterations in intracellular potassium content, changes in catecholamines or adrenergically mediated events, bradykinin, and perhaps a variety of additional hemodynamic, humoral, or metabolic considerations. Whatever the mechanism, it is clear that blood pressure reduction per se does not have a uniform effect on insulin sensitivity. The impact of specific antihypertensive therapy on lipid levels, briefly alluded to above, deserves more detailed consideration.

**Antihypertensive Therapy and Lipids**

An extensive body of literature has developed documenting the effects of antihypertensive drugs on lipids. While informative, these studies have not always provided insight into the mechanisms of these effects. It is not the intent of this review to provide an encyclopedic reference to all reported studies but rather to summarize the consensus of the observations. Diuretics consistently increase the atherogenic lipid components, total cholesterol, triglycerides, and LDL when compared with placebo or baseline measurements. This effect appears to be dose-related and persists for 3-7 years of antihypertensive treatment. Although all subjects beginning the latter study were not followed for the entire 3-year period, consistent lipid alterations were seen at 1, 2, and 3 years. Not only have the benzodiathiazide agents been implicated, but also chlorthalidone and loop diuretics such as furosemide, particularly when given at antihypertensive doses. Indapamide at a dose of 2.5 mg/day has been reported to have no adverse lipid effects, although one study reported an elevation in serum cholesterol with this agent. The reformulation of metolazone with increased bioavailability (Mykrox) was found to raise cholesterol, triglycerides, and LDL while 0.5 mg was given, as was hydrochlorothiazide plus triamterene. In general, diuretics raise triglycerides by about 30% and total cholesterol by 5-15%. Changes of this magnitude have been shown to have a dramatic effect in increasing the risk for coronary artery disease manifestations.

Diuretics can influence lipid components in several ways. The increase in triglyceride concentration may result from a direct effect of these drugs on secretion of very low density lipoproteins and triglycerides, augmented by the hyperinsulinemia and insulin resistance previously described with diuretic treatment. Diuretics also increase catecholamine levels, which in turn stimulate hepatic cholesterol synthesis. Diuretics are not the only antihypertensive agents with known adverse effects on the lipid profile. Blocker-β-adrenergic blocking agents have been shown to consistently raise triglycerides and decrease HDL both potentially atherogenic effects. Little information is available concerning the relation of these adverse effects to a dose of β-blocker, but both selective (β1) and nonselective (β1β2) agents share this property. Blockers decrease hepatic and lipoprotein lipase activity, thus accounting for the increases in plasma triglyceride levels. Although less extensively studied, β-blockers with intrinsic sympathomimetic activity and those with combined α-adrenergic and β-adrenergic receptor blocking properties do not appear to exhibit these adverse effects.
Left Ventricular Hypertrophy

Left ventricular hypertrophy is a frequent concomitant of hypertension, which is not consistently improved with blood pressure control. The major stimuli for hypertensive hypertrophy appear to be pressure and volume overload as well as stimulation of the renin-angiotensin and sympathetic nervous systems. The agents that have most consistently been demonstrated to induce regression of left ventricular hypertrophy have been those that have normalized several of the causative factors without invoking compensatory increases in others. These agents include α-adrenergic blockers, angiotensin converting enzyme inhibitors, calcium channel entry blockers, and some of the centrally acting antisympathetic agents.93–98 The data regarding diuretics have not been consistent as some studies have reported regression of hypertrophy with long-term treatment and others have not.

In summary, hypertension is a major risk factor for cardiovascular morbidity and mortality. Its treatment can reduce these events to inconsistent extents depending on the presence of other risk factors for cardiovascular disease and the impact of specific drugs chosen for lowering blood pressure. The most recent recommendations of the Joint National Committee emphasize the individualization of initial antihypertensive therapy. Current information and the availability of newer antihypertensive agents devoid of many of the potentially adverse side effects of older agents provide the potential for even more effective reduction of cardiovascular morbidity and mortality by treating hypertension than has previously been demonstrated.

Acknowledgment

The author thanks Cassandra Brown for her expert and considerate assistance in the preparation of this manuscript.

Questions and Answers

Dr. Annette Fitz (University of Iowa, Iowa City): Why do you think that clonidine does not decrease left ventricular hypertrophy, since it lowers renin and angiotensin levels as well as heart rate and catecholamines?

Dr. Weinberger: I am not really convinced that it does not. I do not think there is much information on this issue. There are at least two reports suggesting that clonidine may cause regression of left ventricular hypertrophy.97,98 Methyl dopa, a drug that acts in a very similar way to clonidine, has also been demonstrated to induce regression of left ventricular hypertrophy.97 I am just not sure that sufficient studies with clonidine have been conducted to conclusively settle that issue.

Dr. William Lawton (University of Iowa, Iowa City): There has been a great deal of interest in low dose hydrochlorothiazide. If low doses are used to prevent hypokalemia, can the adverse effect on lipids also be prevented?

Dr. Weinberger: There is no question but that the metabolic effects of diuretic therapy are dose-dependent. The blood pressure effects are also dose-dependent. I do not think we have enough information to tell us whether the curves are parallel or superimposable. At doses below 25 mg of hydrochlo-
rothiazide, there is a reduced occurrence of adverse metabolic events. At lower doses of hydrochlorothiazide, when used without any other agents, a beneficial reduction of blood pressure in hypertensive patients is very difficult to consistently demonstrate. There are some new studies that perhaps will give us a better handle on the relative antihypertensive and metabolic effects of low dose diuretic therapy. I think this is an issue about which we need more detailed information.

**Dr. John Stokes (University of Iowa, Iowa City):** Some of the data you presented from the MRFIT study, showing three groups of patients treated with multiple interventions, revealed that the degree of total cholesterol lowering was greater in patients who received no diuretic therapy than in those treated with diuretics alone or combined with \(\beta\)-blockers. Yet, in the next panel of the illustration, this relation did not occur with LDL levels. How can one conclude from those data that treating elevated blood pressure with these agents gives the patient a more adverse lipid profile and thus an increased risk of coronary heart disease?

**Dr. Weinberger:** One of the possibilities is that the LDL measurements were less accurate than were total cholesterol measurements in that study. The methodology to measure total cholesterol 10 or 15 years ago in the MRFIT study, when the study was initiated, was more reproducible than the measurement of LDL, which is actually a calculated rather than a direct measurement.

Second, I would also propose that a simultaneous consideration of HDL levels is very important in assessment of the patient’s risk for cardiovascular disease. As you may recall, those who did not require antihypertensive drugs had a slight rise in HDL levels, so that the cholesterol/HDL ratio changed much more dramatically in that population than in those who received diuretics alone or in combination with \(\beta\)-blockers where a decrease in HDL was observed.

Finally, I should mention that there were different recruitment criteria for patients in the MRFIT study. Patients who did not require antihypertensive drugs had lower blood pressures but smoked or had higher lipid levels than those with higher pressures. Thus, they may not have been directly comparable.

**Dr. Lawrence Hunsicker (University of Iowa, Iowa City):** You have emphasized the possibility that failure of antihypertensive therapy to lower cardiovascular events might be due to balancing adverse metabolic effects. As you know, there has been a recent report that has suggested that the effect of blood pressure lowering might be biphasic with regard to cardiovascular events, with those patients with modest degrees of reduction getting protection and those with more severe degrees having actual increases in the number of untoward events. How do you relate these two theories, and should we be cautious about the degree to which we lower blood pressure?

**Dr. Weinberger:** You have raised a very important point, which I did not discuss—the phenomenon of the J-shaped curve, which has now been addressed in several studies. The observation is that a reduction of diastolic pressure to a level between 80 and 85 mm Hg in hypertensive patients may be associated with an increase in mortality rate. The interpretation of that observation, as far as I am concerned, is still unclear. The most favored view is that these individuals may have unrecognized coronary artery disease, and by reducing diastolic pressure below a critical level, there is a decreased coronary perfusion and an increased risk of myocardial infarction. I think that excessive blood pressure reduction is an important caveat; however, it should not deter us from treating hypertension, particularly in the systolic form, as that has been shown to be an important risk factor for all forms of cardiovascular disease. The possibility that the J-curve phenomenon may be an explanation for the failure of antihypertensive trials to reduce cardiovascular events must be considered.

I would further mention that in the one American study you cited that demonstrated that antihypertensive therapy reduced coronary disease—the HDFP—the component of the HDFP that was more effective in lowering blood pressure was the stepped-care approach, which led to about a 5 mm Hg lower diastolic pressure than that seen in the referred-care group. Again, that is an argument in favor of the benefit of more intensive diastolic blood pressure reduction in hypertensive patients. The J-curve is a possibility that must be considered, but I do not think we have all the answers yet on optimal levels of blood pressure reduction.

**Dr. Fitz:** With respect to \(\beta\)-blockers, since some patients treated with them demonstrate a decrease in sudden death, how do we balance this against the use of other drugs that, although they possess other beneficial effects, do not protect as well against sudden death from myocardial infarction?

**Dr. Weinberger:** I would not propose to make any recommendation for the treatment of acute myocardial infarction, as that is not my area of expertise. My interpretation of the available data is that \(\beta\)-adrenergic blocking drugs are still good initial choices in patients with acute myocardial infarction if they are used in proper doses that afford or confer the beneficial effects against sudden death. The major benefit appears to occur in the first 6 months of treatment. At present, we have no hard data for any of the other antihypertensive drugs confer benefit against sudden death. So I could not advocate replacing \(\beta\)-blockers for initial management of acute myocardial infarction and prevention of sudden death with these other agents. However, the long-term benefits of \(\beta\)-blockers are uncertain at the present time except in comparison with diuretics.
unknown long-term consequences of these newer antihypertensive drugs. By analogy to the latter issue, the hypolipidemic agent clofibrate was associated with excess long-term mortality in a World Health Organization trial despite its lipid-lowering properties.

**Dr. Weinberger:** You have opened up some important and clinically relevant questions. The issue of cost is an important one, particularly today when we are faced with pressures of an economic nature that influence the practice of medicine. I think we must consider cost beyond only the cost to fill a prescription for a single hypertensive drug. For example, in my practice, patients who used to be treated with hydrochlorothiazide alone were almost invariably receiving other drugs to deal with hypokalemia and the increases in sugar, uric acid, and cholesterol. They made more frequent office visits and they had more laboratory tests to follow up on these adverse effects. So cost is a major concern, but we must consider all aspects of antihypertensive therapy. The cost of health care for cardiovascular disease attributable to drugs in 1988 represented less than 6% of the total cardiovascular health care bill. The major costs were not for drugs but for hospitalization, nursing home care, disability, rehabilitation, professional fees, and so on. The broad issue of cost is an important one, but I am not sure that we can address it today.

The issue of compliance also is critically important, because if a patient does not stay on his medication, he will not derive any benefit from it. This is being increasingly addressed by studies investigating the issue of compliance itself and the quality of life. I think we need to learn more about that.

Regarding the long-term effects of the newer agents, we have little data. I think we can say, from the data we do have, that diuretics have not reduced the incidence of coronary artery disease manifestations and sudden death. We have indirect evidence that some of the newer agents may at least have a beneficial effect on some of the factors known to influence these events, and therefore it is possible that they may have a long-term beneficial effect on coronary disease. There may be some long-term disadvantages or side effects of the newer agents, but we cannot address that issue at present because we do not have the data.

**Dr. Lawton:** I would like to ask about β-blockers, especially those with high intrinsic sympathomimetic activity (ISA). Could you comment on their place, as they do not confer cardioprotective effects and there are other antihypertensive agents with less adverse effects?

**Dr. Weinberger:** The role of the ISA-type β-blockers is not well defined at present. The major advantage of them, as I see it, is a lessening of hemodynamic and metabolic “costs” to the patient taking these agents compared with the conventional β-adrenergic blockers. On the other hand, the agents with intrinsic sympathomimetic activity have not been shown to be cardioprotective, and in experimental animals undergoing coronary ligation, infarct size extended in animals receiving pindolol compared with those receiving placebo. Thus, the partial agonist effects of these agents may be a disadvantage in the situation of acute myocardial infarction.

**Dr. Allyn L. Mark** (University of Iowa, Iowa City): You said, in talking about the problems with β-blockers, that they are reported to decrease coronary blood flow, implying a potentially adverse effect. Coronary blood flow is related to both metabolic and coronary vasomotor tone, and decreases in coronary blood flow with β-blockers are likely related to decreases in metabolic demand and may therefore not be adverse.

**Dr. Weinberger:** I mentioned reduction in coronary blood flow in conjunction with similar decreases in regional perfusion involving renal blood flow and cerebral blood flow, which is a common finding with β-adrenergic blocking drugs. As you have correctly pointed out, the decrease in heart rate and the decrease in metabolic demand that is conferred by β-adrenergic blockade may offset the decrease in blood flow, so the net result in terms of angina and in oxygen delivery is generally beneficial, at least for those with reduced heart rate. This may not be the case for those drugs having intrinsic sympathomimetic activity. I did not mean to imply that conventional β-blockers would worsen angina, but we do know that they decrease coronary blood flow as well as renal and cerebral flow, and within that setting, they may be unphysiological in terms of our ultimate hemodynamic goals in the treatment of hypertension.

**Dr. Mark:** You mentioned that β-blockers act almost entirely by decreasing cardiac output. Do you believe, then, that decreases in renin release, longitudinal adjustments in vascular resistance, and central nervous system effects have no role in the antihypertensive or clinical effects of β-blockers in the treatment of hypertension?

**Dr. Weinberger:** The issue of renin release may be a chicken-and-egg phenomenon. β-Blockers reduce blood pressure in patients with elevated renin levels, not necessarily because they reduce renin levels but because the patients have enhanced sympathetic nervous system activity, for which increased renin levels may be a marker. The decrease in renin levels with β-blockade reflects the decrease in adrenergic responsiveness that is also manifested by decreased cardiac output in response to β-adrenergic blockers. The changes in vascular resistance are difficult to evaluate because they are derived parameters based primarily on the fact that blood pressure falls and not based on any demonstration of increased blood flow at peripheral levels. The central nervous system effects of β-blockers are another potentially important factor, but not all of the β-blockers penetrate the brain with equal facility. Yet they all have comparable blood pressure-reducing effects. I tend to reconcile the central nervous system effects of β-blockers to a relatively minor role in the blood pressure response to β-adrenergic blockers.
References


3. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic pressure averaging 90 through 114 mm Hg. JAMA 1970;213:1143–1152.


**KEY WORDS** • lipids • cardiovascular disease • hypokalemia • hyperglycemia • hyperinsulinemia • antihypertensive therapy • atherosclerosis • hypertrophy

*Hypertension* 1990;16:201–211

Presentation and publication of Clinical Conferences are supported by an educational grant from Merck Sharp & Dohme.
Optimizing cardiovascular risk reduction during antihypertensive therapy.
M H Weinberger

_Hypertension_. 1990;16:201-211
doi: 10.1161/01.HYP.16.2.201

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1990 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/16/2/201.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Hypertension_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Hypertension_ is online at:
http://hyper.ahajournals.org//subscriptions/