Antihypertensive Drug Therapy and Coronary Heart Disease Risk

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Coronary heart disease (CHD) is the major cause of death in the United States. Major modifiable risk factors for CHD are hypertension, hypercholesterolemia, and cigarette smoking, with concomitant risk factors, especially left ventricular hypertrophy, that act synergistically to significantly increase overall risk. Antihypertensive therapy, while reducing the incidence of stroke, has not consistently reduced the incidence of CHD. This may be a result, in part, of adverse effects on the metabolic profile, especially on blood lipids, which are induced by diuretics and certain β-blockers. Other antihypertensive agents appear to be either lipid neutral, such as calcium channel blockers and angiotensin-converting enzyme inhibitors, or lipid positive, such as selective α_1-blockers. The choice of initial antihypertensive therapy should be made with all of a patient's risk factors in mind. In addition to the drugs recommended in the *1988 Guidelines of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure*, selective α_1-blockers should also be considered since they improve the lipid profile as well as reduce blood pressure.

Key words. Coronary disease; hypertension; risk factors; antihypertensive agents.
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Despite a decline in its incidence in recent years, coronary heart disease (CHD) is still the major cause of death in the United States. Recent estimates show that 5.4 million cases of CHD are diagnosed each year, with 550,000 deaths resulting annually.[1] Coronary heart disease is associated with $8 billion per year in direct health care costs and $60 billion in total economic costs.[1] Efforts to reduce the incidence of morbidity and mortality from CHD have focused on identifying risk factors and encouraging primary prevention strategies.

Much of the information now known regarding risk factors for CHD comes from data supplied by the Framingham study.[2] The study identified the major modifiable risk factors: hypertension, hypercholesterolemia, and cigarette smoking. In addition, the Framingham data identified a number of other factors that increase the risk of CHD. Left ventricular hypertrophy, defined by specific abnormalities found on electrocardiography or echocardiography, right and left bundle branch block, nonspecific ST and T wave abnormalities in the resting electrocardiogram, and diabetes all increase the odds of developing overt clinical CHD.

A family history of premature CHD places individuals at much higher risk: a person whose father died of CHD before the age of 60 years has twice the risk of developing CHD compared with persons whose parents died after age 60 years.[2] Furthermore, a family history of elevated cholesterol levels means that a person has a 50% chance of also developing hypercholesterolemia, which can triple the risk of CHD before the age of 60 years.[2]

The risk for CHD increases modestly in persons with rising blood glucose levels and increases substantially in persons with diabetes mellitus who have higher glucose levels.[2] Cardiovascular disease risk increases dramatically with central obesity, which is usually accompanied by high blood pressure and elevated blood cholesterol. The risks of myocardial infarction, sudden death, and angina pectoris increase with low-level physical activity.[2] Other risk factors include high levels of stress and low concentrations of cardioprotective high-density lipoprotein cholesterol.

Hypertension was one of the first major risk factors to gain wide public attention. The Framingham study[3] showed that the prevalence of high blood pressure increases with age; nearly one third of the patients between 57 and 63 years of age had hypertension (Figure 1). The Framingham study also showed that compared with nor-

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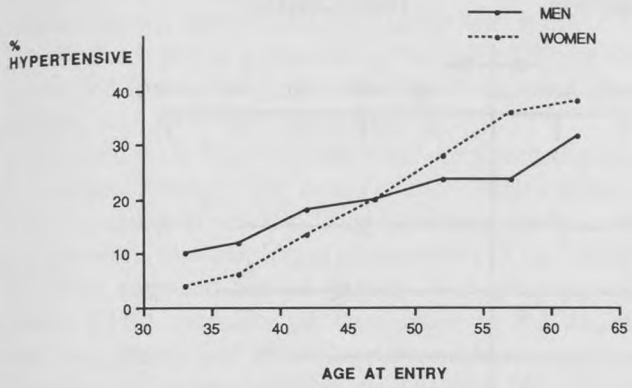

Figure 1. Prevalence of hypertension (systolic/diastolic blood pressure >160/95 mm Hg) in the Framingham study. From Castelli WP, Anderson K. A population at risk. Prevalence of high cholesterol levels in hypertensive patients in the Framingham study. Am J Med 1986; 80(Suppl 2A):23–32. Reproduced with permission.

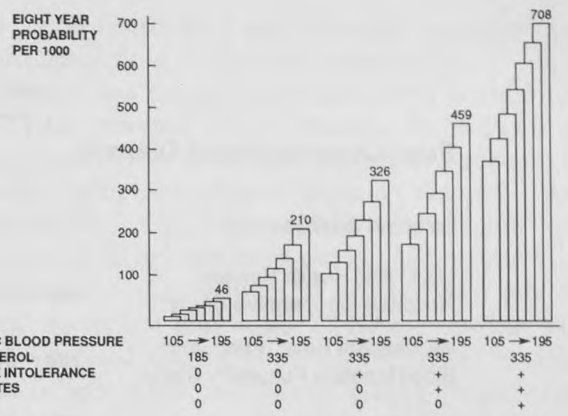

Figure 2. Risk of cardiovascular disease in 40-year-old men according to systolic blood pressure at specified levels of other risk factors. Data are derived from the Framingham study 18-year follow-up. From Castelli WP. Edidemiology of coronary heart disease: The Framingham study. Am J Med 1984; 76(Suppl 2A):4–12. Reproduced with permission.

motensive subjects, hypertensive patients have a twofold to threefold greater incidence of CHD and a sevenfold greater incidence of stroke. The study found that the most common complication of both borderline and definite hypertension is CHD. Although few blacks were included in the Framingham data, other studies have shown that hypertension is more common and more severe in black patients.[3]

Epidemiologic studies have clearly shown that elevated cholesterol levels are a powerful risk factor for CHD.[4–6] Extensive data from the Multiple Risk Factor Intervention Trial (MRFIT)[5] show that as cholesterol levels in patients rise from 180 to 245 mg/dL (4.65 to 6.35 mmol/L), there is a corresponding increase in cardiovascular deaths. Moreover, this association was continuous throughout the range of cholesterol levels in the population studied.[5,6] Risk of CHD increases steadily as cholesterol levels increase, particularly levels >200 mg/dL (>5.15 mmol/L). In the Framingham study, men who developed a myocardial infarction had a baseline mean total cholesterol level of 244 mg/dL (6.30 mmol/L).[4] The investigators found that the level of total cholesterol is closely linked to the incidence of CHD in patients under the age of 50 years.

It is important for clinicians to recognize that concomitant risk factors act synergistically to increase the patient's overall risk for CHD. Increasing blood pressure and rising blood cholesterol levels, for example, exert a powerful synergistic interaction on the development of CHD. In fact, hypertension and hypercholesterolemia often coexist in the same patient, and the greater the rise in blood pressure, the greater the likelihood that a lipid abnormality is present.[4] Similar interactions exist for cigarette smoking, glucose intolerance, and left ventricular hypertrophy. Figure 2 depicts the risk of cardiovascular disease by systolic blood pressure when other risk factors are present. By treating only one risk factor, such as hypertension, patients are not optimally protected from CHD. Management of the patient should include assessment and treatment of all CHD risk factors rather than a single risk factor. Furthermore, in treating one risk factor, physicians must be careful not to adversely affect another. This is particularly true in selecting drugs for antihypertensive therapy, which has not been shown to consistently reduce the incidence of CHD.[7,8]

Effect of Antihypertensive Therapy on the Risk of CHD

Great emphasis has been placed on the detection and treatment of hypertension because it is a major risk factor for cardiovascular disease. Several large-scale trials have demonstrated that aggressive treatment of hypertension reduces cardiovascular morbidity and mortality primarily by reducing the incidence of stroke.[9–14]

In contrast, a positive correlation between aggressive and intensive treatment of hypertension and a reduction in the rate of fatal or nonfatal myocardial infarction has not been consistently found in the major hypertension trials.[7,9,11–20] For example, pooled results for fatal CHD (9 studies) and for nonfatal myocardial infarction (8 studies) were subjected to meta-analysis (Figure 3); the overall mortality rate was 367 cases in the pooled intervention subgroups and 399 in the pooled control groups.[15] According to a meta-analysis of the Hypertension Detection and Follow-up Program[13] and subsets of

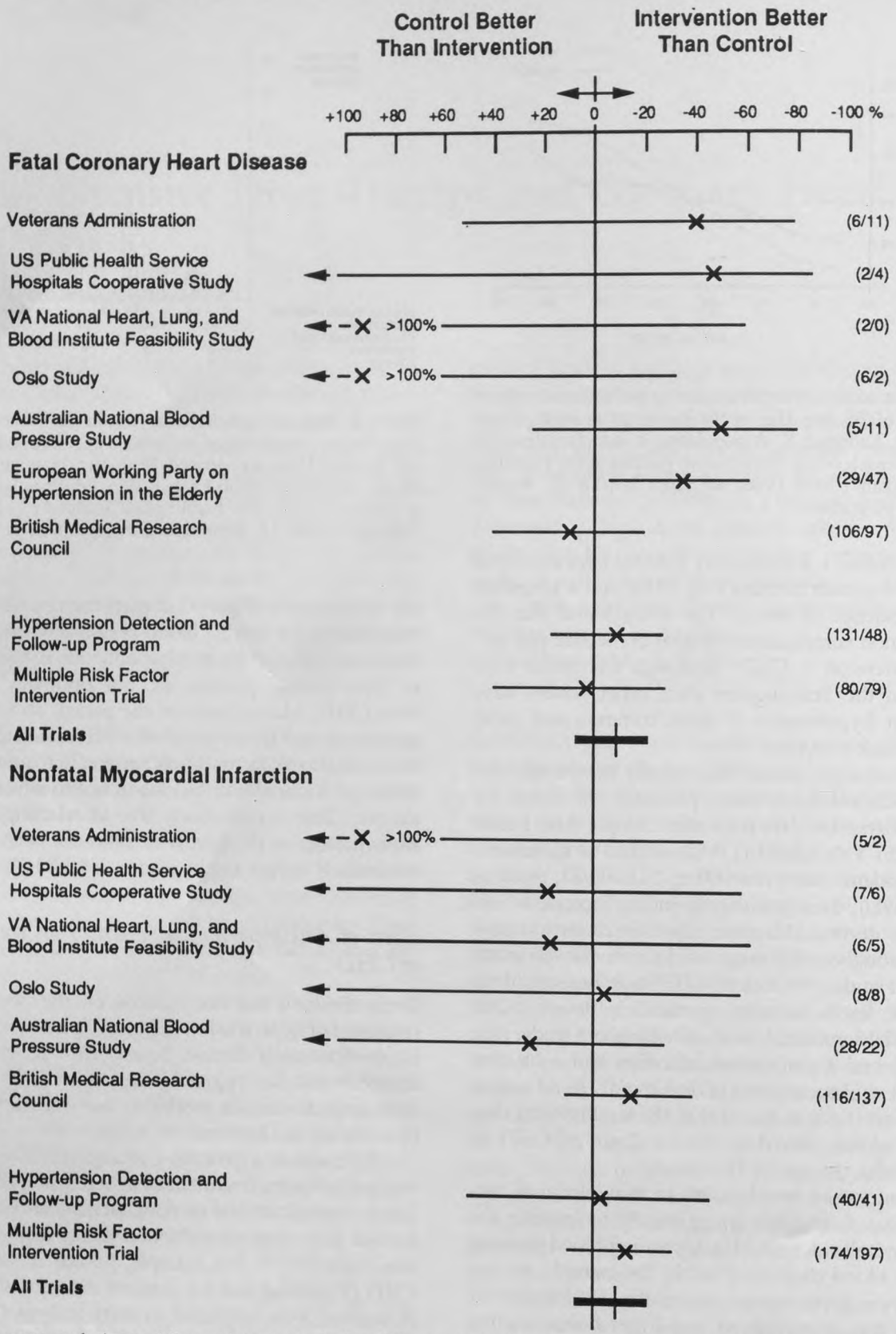

Figure 3. A meta-analysis providing estimates of relative difference in fatal coronary heart disease and nonfatal myocardial infarction between intervention and control group in clinical trials. The bar graph shows estimates (X) with approximate 95% confidence intervals (−) of the relative difference. The numbers in parentheses are the numbers of events (intervention/control). Adapted, with permission, from Cutler JA, MacMahon SW, Furberg CD. Controlled clinical trials of drug treatment for hypertension. A review. Hypertension 1989; 13(Suppl I):I36–44.

patients in two other trials,[19,20] CHD was reduced by 14%,[21] which was approximately one half of the benefit anticipated from short-term lowering of diastolic blood pressure by 5 to 6 mm Hg (Figure 4).[7]

Several early hypertension trials employed diuretics as first-line therapy. In the Veterans Administration study[10] published in 1967, 143 patients with severe hypertension (diastolic blood pressure of 115 to 129 mm Hg) were followed for 18 months. No difference was seen in CHD mortality between those in the diuretic treatment group and those in the untreated group. A later Veterans Administration report[11] on 380 patients with mild to moderate hypertension (diastolic blood pressure 90 to 114 mm Hg) who were followed for an average of more than 3 years also showed no significant effects of treatment on the incidence of myocardial infarction and sudden death. Similarly, in the Public Health Service trial (N = 389),[12] treatment of hypertension did not significantly affect the incidence of CHD.

To obtain statistical proof that treatment of hypertension is beneficial in reducing CHD, the Australian trial[14] followed 3427 patients who had mild hypertension for an average of 4 years. As in previous studies, the incidence of stroke was reduced, but the total number of coronary events, both fatal and nonfatal, was not significantly affected by drug treatment.

The first study to show a relationship between a reduction in the incidence of CHD and antihypertensive therapy was the Hypertension Detection and Follow-up Program.[13] Throughout the United States, 10,940 subjects with high blood pressure were randomly assigned to either the treatment group (intensive antihypertensive treatment beginning with diuretics [stepped care]) or the control group (referred to physicians in the community for usual care). Intensive treatment resulted in 26% fewer deaths from myocardial infarction after 5 years. While these findings seem to suggest that antihypertensive therapy reduces the incidence of CHD, there was no placebo control group; the patients in the referred care group may or may not have received treatment. The lower rate of coronary mortality in the stepped-care group cannot therefore be attributed to differences in blood pressure control alone.

In contrast to the findings of the Hypertension Detection and Follow-up Program, the Oslo Hypertension Study[16] showed that the 5- and 10-year CHD mortality rates were *greater* in mildly hypertensive patients treated with diuretics plus propranolol or methyldopa than in patients in the untreated control group (Table 1). Total mortality in the two groups was similar, the result of more noncardiovascular events occurring in the untreated group. This increase in CHD mortality in patients treated with standard antihypertensive therapy caused concern at the time and prompted reevaluation of standard initial drug therapy for hypertension.

When it was thought that these early studies may have failed to prevent CHD because they focused only on blood pressure control, a new study was instituted to ascertain whether a treatment regimen that took into account multiple CHD risk factors would result in a lowering of coronary mortality and morbidity. The Multiple Risk Factor Intervention Trial[17] involved subjects who had no clinical evidence of CHD at entry but who were at increased risk for developing CHD. The study did not include a placebo control group; instead, randomly assigned patients received aggressive treatment with antihypertensive drugs, dietary measures to reduce weight and blood cholesterol levels, and steps to decrease or eliminate cigarette smoking (special intervention), or were referred to their community physician for risk-factor management (usual care). The patients in the special intervention group received hydrochlorothiazide or chlorthalidone, with reserpine, methyldopa, or propranolol added to control blood pressure as necessary.

Results of the 6-year MRFIT were disappointing. Although patients in the special intervention group reduced their levels of blood pressure, cholesterol, and cigarette smoking, the incidence of CHD was not significantly less than in the control group. Among hypertensive patients, there were 79 deaths in the control group and 80 in the special intervention group. Thus, aggressive treatment of hypertension in this study apparently was no more effective than usual care in reducing CHD mortality.

The failure to establish a link between the treatment of hypertension and an improvement in CHD in the MRFIT may have been due to metabolic disturbances induced by conventional diuretic therapy. For example, patients receiving diuretics showed less reduction in blood cholesterol levels, had an increase in triglyceride levels, and a slight decrease in high-density lipoprotein cholesterol levels as compared with patients not receiving diuretics.[22] The addition of propranolol caused a substantial decrease in high-density lipoprotein cholesterol levels, adding to the risk for CHD in these patients. These lipid disturbances were sustained over 6 years. Furthermore, hypertensive patients with resting electrocardiographic abnormalities at the time of entry into the study who were given diuretics had a higher sudden death rate than those who were not given diuretics.[23] This study therefore raised some provocative issues regarding the proper choice and dosage of drugs to reduce elevated blood pressure, and the interaction of hypokalemia and left ventricular hypertrophy.

In a follow-up of the MRFIT cohort 10.5 years after the study began, the coronary disease mortality rate for

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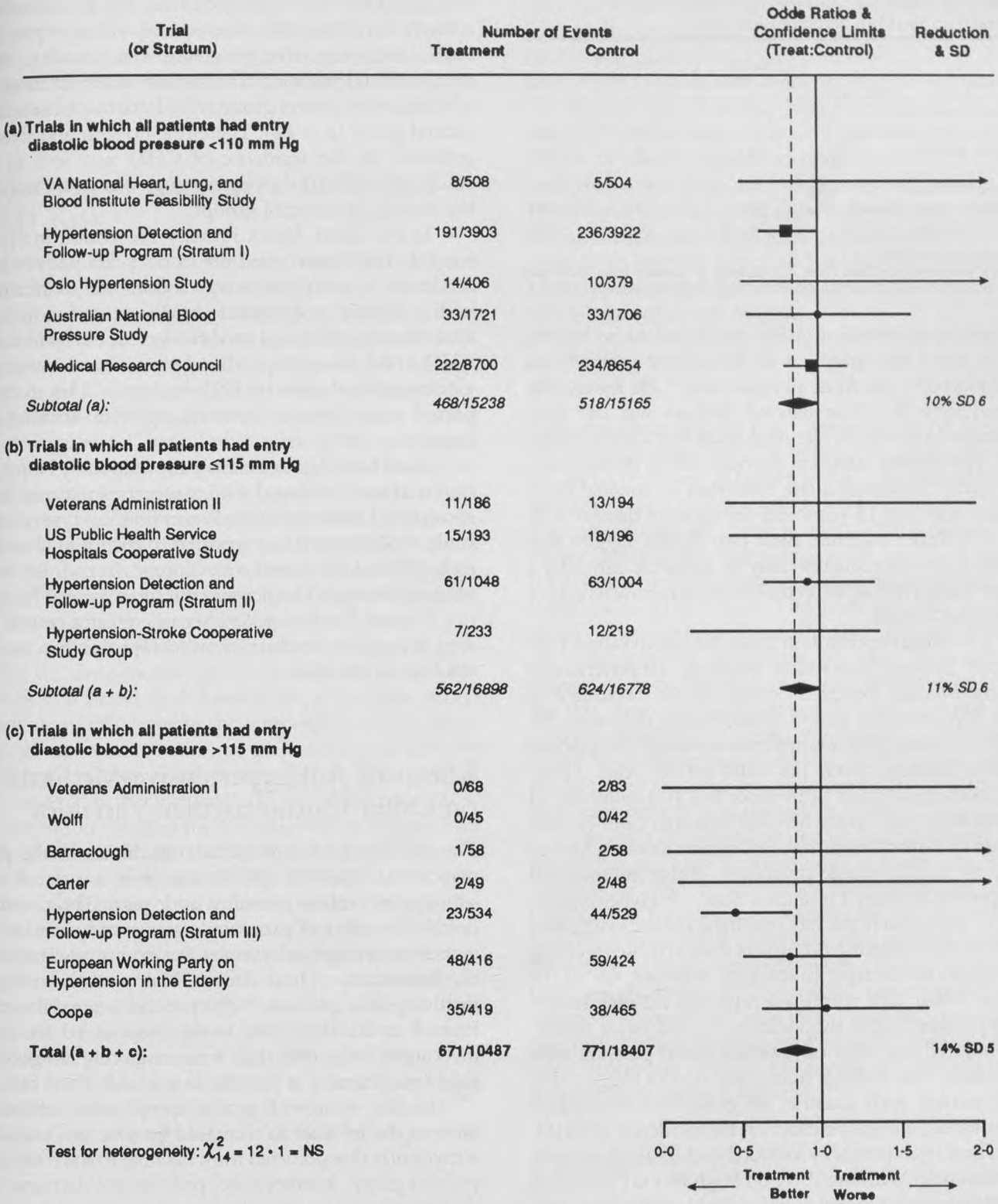

Figure 4. Coronary heart disease in selected antihypertensive trials. Adapted, with permission, from Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke, and coronary heart disease. Part 2. Short-term reductions in blood pressure: overview of randomized drug trials in their epidemiological context. Lancet 1990; 335:827–38.

Table 1. Incidence of Coronary Mortality and Total Mortality in the Oslo Hypertension Study

Mortality	Treated (n = 406)	Control (n = 379)	*P* Value
Five-year mortality			
Coronary heart disease	6	2	NS
Total mortality	10	9	NS
Ten-year mortality			
Coronary heart disease	14	3	<.01
Total mortality	21	20	NS

NS denotes not significant.
Adapted, with permission, from Leren P, Helgeland A. Coronary heart disease and treatment of hypertension. Some Oslo Study data. Am J Med 1986; 80(Suppl 2A):3–6.

the special intervention group was found to be 10.6%, which was lower than that of the control group.[8] The total mortality rate from all causes was 7.7% lower. The main reason for these delayed declines was the 24% reduction in the death rate from acute myocardial infarction. This finding supports the observation of the Coronary Drug Project of a late reduction in nonfatal myocardial infarction 15 years after the onset of therapy with niacin.[24] Taken together, these two studies suggest that benefit from risk reduction may be apparent only after a longer period of follow-up than has been characteristic of most clinical trials.

Two large hypertension trials, the International Prospective Primary Prevention Study in Hypertension[19] and the Medical Research Council on the Treatment of Mild Hypertension trial,[20] showed little difference between treatment with antihypertensive drugs and placebo in total coronary events per 1000 patient years. However, both trials found a difference in CHD endpoints in nonsmoking men. In the Medical Research Council trial, the use of β-blockers in male and female smokers had no effect on cardiovascular endpoints. In the International Prospective Primary Prevention Study in Hypertension, among nonsmokers the rate of critical cardiac events was lower in men receiving β-blockers than in those receiving non–β-blocker therapy. In smokers, however, the rate of critical cardiac care events was higher in the men receiving β-blockers. Thus, the addition of a risk factor (smoking) negated the effect of lowering blood pressure with β-blockers. The findings from these studies suggest that drug therapy with diuretics or β-blockers in smokers might induce a negative effect on the incidence of CHD.

These trials primarily included middle-aged subjects. The European Working Party on High Blood Pressure in the Elderly trial[18] was a double-blind, randomized, placebo-controlled trial carried out in hypertensive patients over the age of 60 years who were assigned to treatment with either a diuretic (hydrochlorothiazide and triamterene) or matching placebo. Methyldopa was added to the active treatment group's regimen if blood pressure remained elevated. Active treatment was associated with a barely significant reduction in fatal cardiac events ($P = .048$, comparing active treatment with placebo). However, nonfatal myocardial infarction occurred more frequently in the control group (n = 19) than in the actively treated group (n = 12). Therefore, no clear and absolute reduction in the incidence of CHD was seen in this study. No difference in lipid values was noted between the treated and control groups.

In the Heart Attack Primary Prevention in Hypertension trial,[25] men aged 40 to 64 years with mild to moderate hypertension were randomized to treatment with a diuretic or β-blocker. After a mean follow-up of 45.1 months, there was no difference in the incidence of CHD in the two groups. Blood pressure was lowered to a comparable degree by both regimens. The study reported no interaction between cigarette smoking and response to either drug.

The Heart Attack Primary Prevention in Hypertension trial was continued with a subset of patients in the Metoprolol Atherosclerosis Prevention in Hypertensives study.[26] Metoprolol was reported to reduce total mortality by 48% as compared with diuretic. In contrast to the Medical Research Council and the International Prospective Primary Prevention Study trials, greater benefit was seen in cigarette smokers given metoprolol than in nonsmokers in this trial.

Effects of Antihypertensive Medications on Other Cardiovascular Variables

The prevalence of ventricular arrhythmias in the postmyocardial infarction patient has been associated with subsequent cardiac mortality and, particularly, sudden death. The effect of propranolol on postmyocardial infarction ventricular arrhythmias was extensively studied in the Beta-Blocker Heart Attack Trial, a multicenter trial involving 3837 patients.[27] The patients entered the study from 5 to 21 days after being hospitalized for acute myocardial infarction and were randomly assigned to either propranolol or placebo in a double-blind fashion.

In the treatment group, propranolol effectively blunted the twofold to threefold increase in ventricular arrhythmias that occurred from baseline to 6 weeks in the placebo group. Furthermore, propranolol decreased the proportion of patients who experienced ventricular arrhythmias while awake vs while asleep. After an average follow-up of 25 months, a 26% reduction in total mortality was seen in the propranolol-treated group compared with the placebo group. The rate of sudden CHD mortality was significantly lower in the treatment group

compared with the placebo group. The conclusion was that propranolol has an antiarrhythmic effect in patients with a recent acute myocardial infarction. This antiarrhythmic effect may have been in part responsible for the reduction in sudden cardiac death seen in this trial.[27]

Reduction of Cholesterol Levels and CHD Risk

Whereas MRFIT examined all risk factors of CHD, the Lipid Research Clinics Coronary Primary Prevention trial[28,29] examined only the effectiveness of interventions in reducing elevated cholesterol levels. Altogether, 3806 men aged 35 to 59 years were enrolled at 12 lipid research clinics in the United States. The enrollees had blood cholesterol levels of 265 mg/dL (6.85 mmol/L) and over, and had no clinical coronary disease at entry. The study was designed to examine whether lowering blood cholesterol levels using cholestyramine therapy and low-cholesterol diet reduces the incidence of myocardial infarction, CHD death, and other coronary events compared with diet control alone. All the men were given a cholesterol-lowering diet; one half were given cholestyramine, a bile-acid sequestrant, and the other half received placebo.

As compared with the placebo-treated group (n = 1900), the drug-treated group (n = 1906) had an 8% reduction in blood cholesterol levels, which was associated with a 19% decrease (placebo deaths = 187, treatment group deaths = 155) in the incidence of CHD.[29] Further evaluation revealed decreases of 20% (287 vs 235 events) in the incidence of angina pectoris, 21% (112 vs 93) in the need for coronary bypass surgery, and 25% (345 vs 260) in the development of a positive exercise electrocardiogram.[28] The decrease in the incidence of CHD was found to have a linear relation to the degree of reduction of low-density lipoprotein cholesterol levels, specifically. These results demonstrated that, in general, for every 1% reduction in cholesterol level, a 2% decrease in CHD incidence could be achieved, thus supporting the causal role of elevated blood cholesterol levels in the pathogenesis of CHD.[28]

Other studies have confirmed this finding and have also shown that diet and drug therapy to reduce lipid levels can lead to a regression or slowing of the progression of CHD.[30–32]

Effects of Antihypertensive Medications on Lipids

The explanation for the lack of a significant decline in the incidence of CHD despite blood pressure reduction with antihypertensive agents is unclear. The Oslo Hypertension Study[16] even suggested a possible increase in cardiovascular death with antihypertensive therapy. It has been postulated that antihypertensive agents employed in the hypertension trials may have a deleterious effect on other CHD risk factors that overrides and obscures the benefit of blood pressure reduction. For example, many antihypertensive drugs are well known to negatively alter blood lipids and lipoproteins, which may contribute to the lack of effect on the incidence of CHD. Since most of these trials used diuretics and β-blockers as initial or secondary therapy, this review will first examine the effects of these drugs on lipids.

Diuretics

Although there is some controversy over their duration of effect, diuretics, the most widely prescribed agents in the initial treatment of hypertension, have generally been shown to have an adverse effect on blood lipids.[33] Short-term and long-term therapy with chlorthalidone and hydrochlorothiazide can significantly increase levels of total cholesterol, low-density lipoprotein cholesterol, and triglycerides (Table 2).[34] The ratio of total to high-density lipoprotein cholesterol is also increased.[35] While the magnitude of these changes may be small, the changes may be sustained over time. However, the data on this issue are controversial.[36] Even minimal lipid changes induced by diuretics may offset any benefit obtained by lowering blood pressure, and this may explain the failure of the large hypertension trials[10,11,17] to demonstrate a reduction in the risk of CHD.[35]

Diuretics are also associated with other adverse metabolic changes. Their primary mode of action is to reduce extracellular fluid volume. The concomitant loss of potassium and resulting hypokalemia has the potential of increasing myocardial irritability, thus inciting ventricular ectopic activity, especially when there is underlying heart disease, such as left ventricular hypertrophy.[37,38] In addition, diuretics can raise blood glucose levels, which can further adversely affect lipid levels.[35] These metabolic disturbances can obscure the benefit of lowering blood pressure in reducing CHD risk.

β-Blockers

As a class, β-blockers also have been shown to adversely influence the lipid profile; they do not appear to significantly affect total or low-density lipoprotein cholesterol levels, but most studies demonstrate increases in levels of triglycerides and decreases in high-density lipoprotein cholesterol levels (Table 3).[38–42] One of the most widely

Table 2. Effects of Diuretics on Lipid Components

Agent	No. of Subjects	Duration	Total Cholesterol (mg/dL)	High-Density Lipoprotein (mg/dL)	Triglycerides (mg/dL)	Low-Density Lipoprotein (mg/dL)
Chlorthalidone	60	6 wk	↑ 19*	↑ 2	↑ 23*	↑ 14
Chlorthalidone	40	1 y	↑ 15†	↑ 1	↑ 36†	—
Hydrochlorothiazide	60	6 wk	↑ 15*	↑ 3	↑ 28*	↑ 9
Hydrochlorothiazide	47	1 y	↑ 12†	↓ 1	↑ 39	—

*P < .05.
†P < .001.
From Weinberger MH. Antihypertensive therapy and lipids: paradoxical influences on cardiovascular disease risk. Am J Med 1986; 80(Suppl 2A):64–70. Reprinted with permission.

studied β-blockers is propranolol, which has been shown to significantly decrease high-density lipoprotein cholesterol levels and increase triglyceride levels in both short-term and long-term studies.[34]

The effect of propranolol on lipids and lipoproteins is potentiated when it is combined with a diuretic. One study demonstrated that the addition of propranolol to polythiazide therapy caused increases in triglycerides and very-low-density lipoprotein cholesterol levels, reduction in high-density lipoprotein cholesterol levels, and reduction in the ratio of high-density lipoprotein cholesterol to total cholesterol.[43] In the MRFIT, further significant reductions in high-density lipoprotein cholesterol levels and increases in triglyceride levels were noted when propranolol was added to a diuretic (both $P < .01$).[22] Similar adverse effects on lipoproteins have been found with atenolol, metoprolol, oxprenolol, and nadolol.[34] However, β-blockers with intrinsic sympathomimetic activity such as pindolol and the combined α- and β-blockers such as labetalol may have a neutral effect on the lipid profile.

Centrally Acting Agents

The centrally acting agents, such as methyldopa and clonidine, effectively lower blood pressure, but data on their effect on lipids and lipoproteins are somewhat con-

Table 3. Effects of β-Blockers on Lipid Components

Agent	No. of Subjects	Treatment Duration	Total Cholesterol, %	High-Density Lipoprotein, %	Triglycerides, %	Low-Density Lipoprotein, %
Propranolol[39]	23	8 wk	NC	↓ 13*	↑ 24*	—
Combined β-blocker study[40]†	53	1 y				
Atenolol			↑ 3	↓ 7‡	↓ 24‡	↓ 5
Metoprolol			↓ 1	↓ 13§	↑ 14‡	↓ 4
Oxprenolol			NC	↓ 11§	↑ 27§	↓ 4
Propranolol			↓ 1	↓ 17§	↑ 51*	↓ 6
Propranolol[38]						
Men	885	3 y	↓ 1‡	—	—	—
Women	880	3 y	↓ 1	—	—	—
Labetalol[41]	35	12 wk	NC	NC	NC	NC
Nadolol[42]	121	12 wk	↓	—	↑ 22‡	—
Pindolol[39]	10	10 wk	NC	NC	NC	—
Oxprenolol[39]	20	5 wk	NC	NC	↑ 22‡	—
Atenolol[39]	20	5 wk	↓ 5‡	NC	NC	—

*P < .001.
†All patients were treated with all drugs for a period of 3 months each.
‡P < .05.
§P < .01.
NC denotes no change.

Table 4. Effect of Centrally Acting Antihypertensive Drugs, Angiotensin-Converting Enzyme Inhibitors, and Calcium Channel Blockers on Blood Lipids

Drug	Lipid Component	Mean Change, %
Guanabenz	Total cholesterol	↓7
	LDL cholesterol	↓14
Clonidine	Total cholesterol	↓8
Methyldopa	HDL cholesterol	↓14
	Total/HDL cholesterol ratio	↑19
Captopril	Total cholesterol	NC
	Total triglycerides	NC
	HDL cholesterol	NC
Nifedipine	Total cholesterol	NC
	Total triglycerides	NC
	LDL, VLDL cholesterol	NC
	HDL cholesterol	NC
Diltiazem	HDL cholesterol	↑15
	Total/HDL cholesterol ratio	↓11

LDL denotes low-density lipoprotein; HDL, high-density lipoprotein; VLDL, very low-density lipoprotein; NC, no change.
Adapted, with permission, from Ames RP. The influence of non-beta-blocking drugs on the lipid profile: are diuretics outclassed as initial therapy for hypertension? Am Heart J 1987; 114:998–1006.

flicting (Table 4).[44] Methyldopa has been shown to decrease high-density lipoprotein cholesterol levels and increase the ratio of total cholesterol to high-density lipoprotein cholesterol.[38] Clonidine and guanabenz are two centrally acting α-adrenergic agonists for which only limited data on their lipid-modifying potential are available. There are reports, however, that total cholesterol levels are reduced when these agents are given alone.[33] Guanabenz may also lower low-density lipoprotein cholesterol levels.[44]

Calcium Channel Blockers

Calcium channel blockers have emerged as primary treatment for many cardiovascular disorders, including angina pectoris, coronary artery spasm, arrhythmias, and more recently, hypertension. In general, these agents do not appear to adversely affect lipoprotein concentrations.[45–49] Verapamil has been shown to decrease low-density lipoprotein cholesterol levels by 12% in patients with angina or hypertension.[45] In one report on diltiazem, a 15% increase in high-density lipoprotein cholesterol levels and an 11% decrease in the ratio of total cholesterol to high-density lipoprotein cholesterol were seen.[46] Although these changes are favorable, more data are required to substantiate this finding. Nifedipine has been shown to have no adverse effect on levels of total cholesterol, low-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol.[47–49] One study on nifedipine reported a decrease of 17% in total triglycerides.[49] Another study with nifedepine noted an increase of 5% to 7% in apolipoproteins AI and AII.[47] Since apolipoprotein A constitutes the major protein component of high-density lipoprotein particles, this change reflects a favorable effect on the lipid profile.

Angiotensin-Converting Enzyme Inhibitors

The angiotensin-converting enzyme inhibitors are currently undergoing extensive clinical investigation, and some reports have been published on their effect on serum lipids.[50] Captopril is the most widely studied and appears to have no adverse effect on total cholesterol, triglyceride, or high-density lipoprotein cholesterol levels. Enalapril has not been as extensively studied as captopril, but in clinical trials it has not been shown to increase total cholesterol levels.[50,51]

Recent studies have focused on the role of insulin in hypertension and the possibility that hypertension may be part of a syndrome of hyperinsulinism, glucose intolerance, obesity, and disturbances in lipid metabolism.[52] Using the euglycemic clamp technique, it has been shown that captopril enhanced insulin sensitivity and tissue glucose utilization by 11%. In contrast, hydrochlorothiazide caused a comparable decrease in these variables.[53]

Selective α_1-Blockers

Selective α_1-blockers such as prazosin, terazosin, and doxazosin effectively reduce blood pressure by means of

Table 5. Effects of Prazosin* on Blood Lipid Levels

	Change, %		No. of Treatment Groups in Which Significant Change Occurred†
	Mean	Range	
Total cholesterol	↓4.3	↑5.8–↓12.5	4/7
High-density lipoprotein cholesterol	↑6.9	↓4.1–↑16.4	4/7
Low-density lipoprotein (plus very-low-density lipoprotein) cholesterol	↓9.5	↑1.7–↓16.8	5/6
Triglycerides	↓8.7	↑6.8–↓16.2	4/6

**N = 199 patients from 6 studies of from 2 to 12 months in duration involving 7 treatment groups.*
†P < .05, change from baseline.
From Leren P. Comparison of effects of lipid metabolism of antihypertive drugs with alpha- and beta-adrenergic antagonist properties. Am J Med 1987; 82(Suppl 1A): 31–5. Reprinted with permission.

Table 6. Effects of Doxazosin on Blood Lipids and Lipoproteins

Study	No. of Patients	Year	Triglycerides, %	Total Cholesterol, %	HDL Cholesterol, %	HDL Cholesterol/ Total Cholesterol Ratio, %
Pool[57]	142	1987	↓9.1	↓1.2	↑7.6	↑8.9
Trost et al[58]	14–19	1987	↓17.4	↓6.1	↑13.0	↑19.7
Frick et al[59]	46	1987	↓5.9	↓1.6	↑7.2	↑8.7

HDL denotes high-density lipoprotein.
Adapted, with permission, from Hansson L. Implications of doxazosin therapy on risk of coronary heart disease. Am Heart J 1988; 116:1832–7.

their selective α_1-adrenergic receptor antagonist effect. Significantly, this effect has also been associated with favorable changes in the lipid profile. Prazosin has been extensively studied and has been shown to decrease levels of total cholesterol, low-density lipoprotein and very-low-density lipoprotein cholesterol, and triglycerides while increasing levels of high-density lipoprotein cholesterol (Table 5).[54] Similar results have been described for terazosin.[55]

In clinical studies ranging from single-dose administration to treatment for more than 1 year, doxazosin has been found to be an effective antihypertensive agent when given alone or with other medications.[56] In addition, a consistent pattern has emerged in the effect of doxazosin on lipoproteins in clinical trials.[57–59] As shown in Table 6, doxazosin therapy is associated with reductions in levels of triglycerides and total cholesterol and with increases in levels of high-density lipoprotein cholesterol and in the ratio of high-density lipoprotein cholesterol to total cholesterol.[60] Experimental data suggest that this agent may have a direct inhibitory effect on intracellular cholesterol production independent of the low-density lipoprotein receptor.[61] Selective α_1-blockers therefore appear to be an attractive new initial therapy to control hypertension without adversely affecting lipids.

Conclusions

Despite comprehensive preventive efforts, CHD remains the primary cause of death in the United States. Unfortunately, lowering blood pressure by antihypertensive therapy has not substantially and consistently reduced the incidence of CHD. In fact, traditional therapeutic agents may adversely affect other CHD risk factors while controlling hypertension. These agents vary considerably in their individual impact on the lipid profile and other CHD risk factors. Diuretics, which have been the mainstay of antihypertensive treatment, adversely affect lipoprotein metabolism. Treatment with β-blockers also produces an adverse effect on blood lipids, which worsens when the drugs are taken in combination with diuretics. Currently, the limited data available on the effects of calcium channel blockers and angiotensin-converting enzyme inhibitors on blood lipids suggest that these drugs are lipid neutral. Preliminary data on the effects of α_1-blockers suggest that these agents may have a favorable effect on blood lipids.

The choice of therapy for the hypertensive patient should be made on an individual basis with careful attention to the effect of antihypertensive drugs on risk factors for CHD. Current knowledge should direct physicians to use therapeutic approaches that reduce blood pressure while improving or at least not adversely affecting the lipid profile. By effectively reducing blood pressure, and at the same time improving the lipid profile, selective α_1-blockers may be an excellent choice in patients at high risk for CHD and merit consideration for approval as first-line drugs in the treatment of hypertension.

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