RISK FACTORS IN THE MANAGEMENT OF THE UNIQUE HYPERTENSIVE PATIENT

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Although there is abundant evidence that antihypertensive therapy decreases the incidence stroke, congestive heart failure, and renal failure, there is conflicting data regarding its effect in reducing coronary artery disease (CAD). Several studies, including the Veterans Administration (VA) trials, the Oslo Study, the Australian Therapeutic Trial, the Multiple Risk Factor Intervention Trial (MRFIT), and the recent Medical Research Council Trial (MRC), have failed to show significant reduction of CAD with antihypertensive therapy.[1-6]

Hypertension is one of several risk factors associated with the development of CAD (Table 1). Although it is one of the major risk factors, only 10 percent of hypertensive patients have hypertension as the only risk factor.[7] It has been suggested that the failure of antihypertensive therapy to reduce the incidence of CAD may be due to the adverse effects of many antihypertensives on other cardiac risk factors.[8,9] Thus, the deleterious effect of these agents on cardiac risk factors other than hypertension is hypothesized to counter the protective effect produced by their blood pressure reduction.

TRIALS OF ANTIHYPERTENSIVE THERAPY AND CARDIOVASCULAR EVENTS

The major clinical trials monitoring the effect of antihypertensive therapy on cardiovascular morbidity and mortality are listed in Table 2. The first of these trials, the VA Cooperative Study Group, was reported in two separate articles.[1,2] The study ended prematurely (two years earlier than planned) in patients with diastolic blood pressure greater than 115 mm Hg when the placebo group showed a dramatic increase in morbidity and mortality compared with the treated group.[1] The study was continued in patients with diastolic blood pressure less than 115 mm Hg.[2] A significant reduction in total cardiovascular events and the incidence of strokes was noted in both the mild and more severe hypertensive groups. The reduction in the incidence of coronary artery events failed to reach statistical significance.

The Hypertension Detection and Follow-up Program (HDFP) trial, a large study of almost 11,000 patients, has been criticized because of an ethical decision not to use a placebo control group.[10] However, this study also showed both statistically and clinically significant decreases in total cardiovascular mortality and total stroke deaths (Table 2). Furthermore, this was one of two studies demonstrating a reduction in CAD mortality with antihypertensive therapy.

The European Working Party on High Blood Pressure in the Elderly (EWP) trial was the only other study to show protection against CAD with antihypertensive therapy.[11] This study was performed in patients aged >60 years and showed a significant reduction in death from myocardial infarction, although nonfatal myocardial infarctions occurred more frequently in the treated group (12 vs 19). Surprisingly, in the trial, the incidence of stroke was not decreased by treatment.

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TABLE 1. CARDIAC RISK FACTORS

Treatable
Cigarettes
Hypertension
Hypercholesterolemia
Diabetes mellitus
Major But Untreatable
Family history of early myocardial infarction
Age
Male sex
Minor Risk Factors
Coronary-prone personality
Obesity
Sedentary lifestyle

The Australian trial was conducted in previously untreated subjects with mild hypertension (blood pressure between 95 and 109 mm Hg) who had no evidence of end-organ disease.[4] Two thirds of the trial end points were secondary to CAD events. The treated group had fewer trial end points than the placebo group (P = .051). Myocardial infarctions occurred in only two patients on active treatment and in eight treated with placebo.

The Medical Research Council (MRC) trial was the latest (and largest) trial.[6] In addition to comparing the effect of treatment vs placebo, it also compared the efficacy of a thiazide diuretic (bendrofluazide) with the beta blocker propranolol in preventing cardiovascular morbidity and mortality. As with the other studies, the incidence of strokes was decreased (although notably not in the subgroup of smokers treated with propranolol), but the incidence of coronary artery events was not. A surprising finding was that propranolol (like bendrofluazide) was ineffective in preventing coronary artery events, except in the nonsmoker subgroup (Table 3).

The Oslo and MRFIT studies raised concerns by suggesting an increase in CAD mortality in the treated subjects.[3,5] In the Oslo study, however, there were too few deaths. Only young (aged 40 to 49 years) asymptomatic subjects, without end-organ disease, were recruited. In fact, only 41 deaths occurred even after 10 years of follow-up. The study reported a significant decrease in stroke morbidity; however, it reported a statistically insignificant increase in coronary artery events in the treated group (Table 2).

The MRFIT has been interpreted as showing that patients with abnormal electrocardiograms (ECGs) who were aggressively treated (strict intervention group) had a higher incidence of CAD deaths (especially sudden death) than a similar group who were referred back to their usual means of medical care (usual care group). The conclusions of the study, however, have been questioned for the following reasons: First, it was actually not a trial of antihypertensive therapy, but was designed to evaluate whether intervention in a number of risks (hypertension was only one of them) would prevent cardiovascular disease. Both the treated and the control groups had similar risk factors and mortality reduction (Table 2). Second, the conclusion that there was an increase in coronary artery disease in the strict intervention subjects was based upon questionable statistical analysis (post hoc subgroup analysis). Finally, the higher mortality reported for the strict intervention group may be an artifact of the unexpectedly low mortality reported in the usual care group.

EFFECT OF ANTIHYPERTENSIVES ON CARDIOVASCULAR RISK FACTORS

Therefore, while hypertension is a known risk factor for coronary artery disease, questions remain as to whether antihypertensive therapy prevents CAD morbidity and mortality. We need to note, however, that the question is not whether antihypertensive therapy improves or prevents other complications of hypertension such as strokes, congestive heart failure, left ventricular hypertrophy, or peripheral vascular occlusive disease, but whether it prevents coronary artery disease. If therapy does not prevent coronary disease, an additional concern is whether lack of protection is secondary to an adverse drug reaction, such as an adverse effect on other cardiac risk factors.

The only known treatable risks in Table 1 that might be altered by drug therapy and contribute to CAD mortality and morbidity are plasma lipids and glucose tolerance. Additionally, diuretic-induced hypokalemia has been implicated in excess cardiac mortality.[12]

Thiazides

Thiazide diuretics have been shown to increase serum cholesterol, precipitate glucose intolerance, and lower serum potassium. Thiazides increase total serum cholesterol and the atherogenic LDL-cholesterol, and they lower the HDL-cholesterol to total cholesterol ratio.[8,9,13–15] Furthermore, the adverse ef-

TABLE 2. EFFECT OF ANTIHYPERTENSIVE THERAPY ON CARDIOVASCULAR MORBIDITY

Trial	Total No. of Cardiovascular Events		No. of Strokes		No. of Coronary Artery Events	
	Control	Treat	Control	Treat	Control	Treat
Veterans Administration (I) (n = 143)	27	2*	4	1	2	0
Veterans Administration (II) (n = 380)	76	22	20	5	13	11
Hypertension Detection and Follow-up Program (n = 10,940)	240	195*	52	29*	69	51*
Oslo (n = 785)	34	25	7	0*	13	20
Australian (n = 3,427)	127	91*	25	12*	88	70
Multiple Risk Factor Interventions Trial** (n = 8,012)	—	—	—	—	79	80
Medical Research Council (n = 17,245)	351	286*	109	60*	234	222
European Working Party (n = 840)	117	68*	22	16	29	17*

* $P \leq .05$
** Data reported as mortality only

TABLE 3. PROPRANOLOL VS THIAZIDES IN PRIMARY PREVENTION OF CORONARY ARTERY DISEASE IN HYPERTENSIVES*

	Cerebrovascular Accidents		Myocardial Infarctions	
	No.	Rate**	No.	Rate**
Placebo	109	2.6	234	5.5
Bendrofluazide	18	0.8***	119	5.6
Propranolol	42	1.9	103	4.8

* Medical Research Council Trial
** Rate per 1,000 patient years
*** $P < .05$

fect on plasma lipids will occur even at doses of hydrochlorothiazide as low as 12.5 mg/d (Table 4). Recent evaluations of data from long-term trials, however, suggest that the detrimental effects of thiazides on plasma lipids may be transient (Table 5). Thus, serum cholesterol appears to return to pretreatment levels or lower after one to two years of chronic therapy.

The thiazides, like other diuretics, will increase urinary loss of potassium. Although other explanations are also plausible, diuretic-induced hypokalemia has been implicated as a cause of sudden death in the Oslo and the MRFIT studies, presumably by precipitating arrhythmias. There are several studies suggesting an increase in premature ventricular contractions (PVCs) on Holter monitor associated with hypokalemia and diuretic therapy.[12,21] However, other studies have failed to confirm the arrhythmogenicity of thiazide diuretics without extreme decreases of serum potassium ($K < 3.0$), and no study has directly implicated thiazides (or, for that matter, isolated PVCs) with increased mortality.[22–24]

Glucose intolerance has also been attributed to diuretic therapy.[25] The glucose intolerance associated with these agents results from the drug-induced hypokalemia, which can be corrected with potassium replacement.[25,26]

Sympatholytics

Therapy with most beta blockers (the most studied being propranolol and metoprolol) is associated with a decrease in HDL-cholesterol, usually with little effect on LDL-cholesterol (Table 6).[8,9,14,18,19] Whereas there is evidence that the thiazide-induced alterations in plasma lipids resolves with chronic therapy, the

TABLE 4. MEAN VALUES* DURING PLACEBO AND HYDROCHLOROTHIAZIDE (HCTZ) STUDY PERIODS**

Valuables	Placebo	HCTZ 12.5 mg/d	HCTZ 112.5 mg/d
Blood Pressure (mm Hg)			
Sitting systolic	168 (15)	152 (26)	136 (15)
Sitting diastolic	98 (6)	90 (14)	88 (10)
Electrolytes (mEq/L)			
Potassium	4.5 (0.5)	4.6 (0.8)	3.8 (0.3)
Sodium	141 (3)	144 (6)	141 (2)
Chloride	105 (3)	104 (3)	102 (3)
Lipids			
Cholesterol	209 (47)	234 (34)	235 (42)
Triglycerides	95 (28)	103 (45)	104 (42)
HDL-cholesterol	65 (16)	56 (14)	68 (21)
Apo A1	141 (14)	127 (16)	131 (14)
LDL-cholesterol	125 (48)	153 (33)	147 (40)
Apo A1	105 (25)	135 (21)	124 (26)
VLDL-cholesterol	19 (6)	21 (9)	20 (8)
Cholesterol/HDL ratio	3.8 (1.2)	4.7 (1.0)	4.3 (1.5)

* ±SD
** From McKenney, et al[15]

TABLE 5. COMPARISON OF SHORT VS LONG-TERM CHANGES IN SERUM CHOLESTEROL INDUCED BY THIAZIDES AND BETA BLOCKERS

Study		Total Serum Cholesterol (TC) (mg/dL)				
		Pretreatment	3 Mos	1 Yr	3 Yr	6 Yr
VA (1980)[16]	THZ	203.1		213.0*	—	—
n = 610	PLCB	196.5		196.4	—	—
Oslo (1978)[13]	THZ	278		—	279	—
n = 300	PLCB	272		—	270	—
EWPHE (1982)[17]	THZ/TMP	250.8		247.7	—	—
n = 335	PLCB	253.3		243.1	—	—
n = 90	THZ/TMP	255.6		—	238.3	—
	PLCB	259.4		—	238.6	—
Berglund (1981)[18]	THZ	267		263	—	255
n = 106	PPL	271		263	—	255
VA (1982)[19]	THZ	226.2	231.1	223.3	—	—
n = 240	PPL	222.3	217*	217.5*	—	—
HDFP (abstract)[20]	TC	Significantly increased at 6 months Unchanged from baseline at 2 years Begins to decrease from years 2–5				

* $P < .05$
THZ, thiazide; TMP, triampterene; PPL, propranolol; PLCB, placebo

reduction of HDL-cholesterol with beta blockers apparently does not.

Beta blockers that have not been reported to alter plasma lipids are pindolol and labetalol. The intrinsic sympathomimetic activity (ISA) of pindolol explains its lack of effect on lipids.[27] Labetalol also appears not to adversely affect plasma lipids.[28–30] It has some ISA, and in addition, has prazosin-like selective alpha-1 blocking activity. Prazosin lowers total cholesterol and LDL-cholesterol and increases both HDL-cholesterol and the HDL-cholesterol to total cholesterol ratio.[8,9,14,31]

TABLE 6. EFFECT OF ANTIHYPERTENSIVE THERAPY ON PLASMA LIPIDS

Agent	Cholesterol			
	Total	HDL	LDL	TG
Thiazide	inc*	nc*	inc	inc
Beta blocker				
Without ISA**	nc	dec*	nc	inc
With ISA	nc	nc	nc	nc
Alpha blocker	dec	inc	dec	—
Alpha/beta blocker	nc	nc	nc	nc
Centrally acting sympatholytics	nc	dec	dec	inc
Reserpine	nc	nc	nc	nc
Angiotensin-converting enzyme inhibitors	nc	nc	nc	nc
Calcium channel blockers	nc	nc	nc	nc

* nc, no change; dec, decrease; inc, increase
** Intrinsic sympathomimetic activity

There are few studies evaluating the effect of the sympatholytic antihypertensive agents such as the centrally acting methyldopa, clonidine, and guanabenz, or the peripherally acting reserpine and guanethidine.[31,32] The studies generally show that these agents have clinically insignificant effects on plasma lipids. Although, in a small study, methyldopa significantly decreased HDL-cholesterol and increased the total to HDL-cholesterol ratio.[8]

Vasodilators

The vasodilator hydralazine and the angiotensin-converting enzyme inhibitors captopril and enalapril have not been shown to adversely affect cardiac risk factors.[31-33] The calcium channel blockers, verapamil, nifedipine and diltiazem, produce insignificant effects on plasma lipids.[34] However, they have been reported to inhibit insulin release in high doses.[25,34]

CONCLUSIONS

Currently, there is insufficient data to determine whether the choice of antihypertensive agents alters the risk for the development of CAD other than by their effect on blood pressure. It is specifically recommended, however, that all cardiac risk factors be monitored periodically during antihypertensive therapy and treated if appropriate (Table 7). Treatment of these risk factors should include the consideration of alternative antihypertensive therapies, if appropriate. Glucose intolerance in patients on diuretic therapy may respond to potassium supplementation.

TABLE 7. GUIDELINES FOR MANAGING CARDIAC RISK FACTORS IN HYPERTENSIVES

Pretreatment assessment of all cardiac risk factors is essential and should be managed aggressively
Normokalemia should be maintained in patients
- on cardiac glycosides
- with a history of arrhythmias
- with symptomatic angina or congestive heart failure
- who develop glucose intolerance on therapy

Diuretic-induced hypokalemia should be treated in asymptomatic hypertensives if <3.0
Antihypertensive-induced alterations in plasma lipids are usually reversible within 12 months. If they persist despite dietary intervention, a change in antihypertensive regimen may be considered

While there is little evidence to suggest that mild hypokalemia (K < 3.0) is detrimental in most hypertensives, it should be avoided in those on cardiac glycosides with a history of arrhythmias and, probably, in those predisposed to arrhythmias (ie, patients showing ECG evidence or symptoms of cardiac ischemia or congestive heart failure). In most hypertensives, the choice of an antihypertensive agent will continue to depend upon the traditional criteria of efficacy in lowering blood pressure, tolerability, cost, and convenience.

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