Controlled trials have made it clear that drug treatment reduces the morbidity of hypertensive disease, in severe (51) and in mild to moderate hypertension (2,15,19,33,37,46,50,52). There was a clear reduction in the frequency of stroke, heart failure, hypertensive encephalopathy, renal failure, and dissecting aneurysms but was ineffective in reducing the frequency of atherosclerosis or its complications, with two possible exceptions. In the MRC study (37) propranolol may have reduced the frequency of myocardial infarction in a subgroup of males who did not smoke. Even if accepts the post hoc analysis as reasonable, the effect was limited. A second exception, a study in the elderly, designed to avoid thiazide-induced electrolyte disarray, documented a reduction in death both from heart disease and from myocardial infarction (2).

Why the disappointing lack of impact of antihypertensive therapy on coronary events? One view is that the expectation was unreasonable (24, 30,55): The trials examined an older population in whom coronary artery disease was already well established, the trials ran for only for a few years. More disturbing is the contention that the therapy might have contributed to risk. Diuretics have been employed in every major trial, and more recently beta blockers have been widely used. Both exert potentially adverse effects on lipid and carbohydrate metabolism. The arrhythmogenic potential of electrolyte disarray induced by diuretics has also concerned many. Left ventricular hypertrophy(LVH) is a risk factor for coronary events, and for susceptibility to arrhythmias: the agents often employed may not reverse LVH.

The major risk factors for coronary heart disease are widely recognized (24). Many occur with increased frequency in hypertension.
I. LVH AS A RISK FACTOR: Although long recognized as important the advent of echocardiography, which provides a more sensitive and specific index (7,27) has kindled renewed interest. A 5-fold increase in morbidity related to myocardial infarction, angina pectoris, stroke and sudden death (7, 22) occurs with LVH. LVH increases with age and with obesity (7,22,27,34). Many hypertensives are sufficiently overweight (13) to contribute to LVH. Few studies on the development of LVH in hypertension, or its reversal with therapy, have examined the influence of obesity as a variable. Individual antihypertensive agents vary in their ability to reverse LVH (8,14,26). Elements beyond blood pressure reduction are important (19). Vasodilators and diuretics are ineffective or minimally effective in reversing LVH (8,14,26). Given the striking ability of centrally acting antihypertensive agents to reverse LVH, it has been surprising that beta-adrenergic blocking agents have proven inconsistent. ACE inhibitors and calcium channel blocking agents are effective (1,18,38).

LVH is an antecedent to congestive heart failure. The unequivocal success of antihypertensive regimens in patients with severe hypertension has not been paralleled by equivalent success in milder hypertension, especially in the elderly (54). One possibility is that the failure to select antihypertensive agents that prevent or reverse LVH has contributed to late heart failure.

The increase in sudden death associated with LVH (21) suggests a predisposition to ventricular arrhythmias (31, 35). Complex ventricular arrhythmias occur (31) without diuretic use or hypokalemia. Electrolyte disarray secondary to diuretic use can contribute to ventricular irritability and sudden death.

II. DIURETIC-INDUCED ELECTROLYTE DISARRAY AS A RISK FACTOR

Multiple observations suggest that potassium and magnesium deficits predispose to cardiac arrhythmias, especially during the evolution of myocardial infarction. Lines of investigation have included the frequency of ventricular premature contractions in diuretic-treated patients, the frequency in large trials of untoward events in patients treated with and without diuretics, and the frequency of ventricular arrhythmias and death in patients who are hypokalemic during acute myocardial infarction.