Heart disease (CHD). To account for the discrepancy between blood pressure and/or beta receptor antagonists had untoward effects on carbohydrate and lipid metabolism that tended to mitigate their beneficial effects on blood pressure. Likely to be of greater relevance is the fact that patients with BP, as a group, tend to be insulin resistant, hyperinsulinemic (~1), dyslipidemic; changes that increase risk of CHD. For example, patients with BP and electrocardiographic evidence of ischemic heart disease are IR, glucose intolerant, hyperinsulinemic (~1), and dyslipidemic when compared to a matched group of patients with normal electrocardiograms. In addition, in patients with BP and asymptomatic atherosclerosis, intima-media thickness (IMT) as assessed by B-mode ultrasonography of the carotid artery was significantly correlated with IR, the height of the plasma glucose and insulin responses to a glucose challenge, and low HDL-cholesterol concentration. Degree of IR was the strongest risk, followed by a low HDL-cholesterol concentration, and systolic blood pressure; these three factors accounted for 55% of the differences observed in carotid artery IMT. Finally, the magnitude of the abnormalities in insulin, glucose, and lipoprotein metabolism when present in patients with BP is much greater than the untoward effect of any anti-hypertensive treatment, and lowering blood pressure with anti-hypertensive treatment does not return these metabolic abnormalities to normal. Since no attention was directed toward these metabolic abnormalities in any clinical trial, it is not surprising that CHD risk reduction was less than anticipated.

Key Words: Hypertension, insulin resistance, hyperinsulinemia, dyslipidemia, glucose intolerance, coronary heart disease.

The purpose of treating high blood pressure is to reduce the risk of complications such as stroke and myocardial infarction. In the absence of evidence from clinical trials, observational studies have raised questions about the safety and efficacy of short-acting calcium antagonists. In case-control and cohort studies of hypertensive patients, calcium antagonists have been associated increased risks of myocardial infarction, congestive heart failure, gastrointestinal bleeding, cancer and total mortality. Well-conducted observational studies should meet specific criteria that include: (1) complete ascertainment of events; (2) a properly chosen control group; (3) comparable assessment of exposures and confounders; and (4) appropriate control for confounding. What distinguishes randomized trials from observational studies is the process by which therapies are assigned, and special forms of confounding by indication are possible when routine care replaces randomization. Several approaches, including comparisons with therapies having the same indications, are available to assess and control for confounding by indication. While the hypothetical effects of putative "unmeasured confounding factors" are often cited as reasons for simply ignoring the findings of observational studies, it is possible to show empirically that these effects are likely to be small unless the confounding factor is at once a major risk factor for the outcome and is, at the same time, strongly associated with the exposure of interest. Observational studies are particularly important for assessing rare but serious side effects of commonly used therapies. While randomized trials are essential for defining the efficacy of drug therapies, observational studies are generally adequate to raise concerns about safety.

Key Words: Research methods; causality; case-control; cohort; experimental; non-experimental.