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Antihypertensive Drugs and Prevention of Atherosclerotic Stroke

J. DAVID SPENCE, M.D., FRCPC, FACP

THE DRAMATIC DECLINE IN STROKE incidence in North America (approximately 60% in the past 15 years) has provoked much debate about the reasons for the decline. The role of the treatment of blood pressure in the reduction of stroke in general, and intracerebral hemorrhage in particular,¹ has been a focus of the debate. Our recent experience highlights the need to pay attention, in future, to those effects of antihypertensive drugs which may affect atherosclerosis, and supports the hypothesis, put forward in 1975 by Russell, that the strokes prevented by treatment of hypertension are hemorrhagic and lacunar strokes, but not those due to atherosclerosis.²

Beginning in 1978, a large hypertension identification and followup program was conducted involving over 32,000 patients in 34 practices.³ This program has apparently led to an unusual degree of awareness of hypertension in the region, with the result that a survey of the surrounding area in 1983–84 showed an unprecedented degree of blood pressure control in the population of Middlesex County: 94% of hypertensives had been detected, 92% were on treatment, and 84% were controlled.⁴ During the same time period, a dramatic change occurred in the number and type of strokes admitted to the largest (850 beds) of the community referral hospitals serving the region, in which is located a very busy Neurology service, and a large aggressive hypertension clinic. From 1977 to 1984 (a time frame chosen because by 1977 a CT scanner had been in operation for a year, and CT had become a routine part of a stroke evaluation in the neurology unit) the number of stroke patients admitted annually declined from 500 to 250. Even more interesting was the change in the type of stroke seen, according to a tabulation done by querying the computerized data base for discharge diagnostic codes: the proportion of strokes due to hypertension (hypertensive hemorrhage and hypertensive lacunar infarction) declined from 50% to 10% of patients, while the proportion of strokes due to atherosclerosis increased from 35% to 70%. (Unpublished data obtained from Victoria Hospital Medical Records statistics).

It appears, therefore, that the problem of hypertensive stroke can be solved, at least in communities with effective blood pressure control, and we must begin to turn our attention to prevention of atherosclerotic strokes. In this context, it is appropriate to ask the question: do antihypertensive drugs prevent atherosclerosis, retard the progression of atherosclerosis, or reduce the complications from atherosclerosis? This

issue has recently been reviewed extensively,^{5,6} and will be discussed briefly here.

Numerous large controlled trials have established that the treatment of hypertension reduces the risk of death, stroke, congestive heart failure, and renal failure.^{7–9} Failure to distinguish between strokes due to hypertensive small vessel disease, and strokes due to atherosclerosis has led to some confusion about the benefits of treating hypertension, and to the mistaken assumption that because hypertension is a risk factor for atherosclerosis, then treatment of hypertension should prevent atherosclerosis and its complications. However, when the prevention of myocardial infarction (a cleaner atherosclerotic complication than stroke) is used to examine this hypothesis, it is apparent that very few hypertension treatment programs were effective in preventing atherosclerotic complications,^{9,10} and in some programs the rate of death from myocardial infarction actually increased with thiazide diuretics.^{11,12} It now appears likely that some antihypertensive drugs may have effects apart from the lowering of blood pressure, which may render them more effective in preventing atherosclerosis. A little-noticed anomaly in the results of the Gothenburg study¹⁰ deserves further attention: in that large study, treatment of hypertension with beta-blockers was effective in significantly reducing death from myocardial infarction, but there was no significant reduction in stroke, perhaps because by modern standards, the treatment goal of 160/95 was rather high. This study raised the possibility that beta-blocking drugs may have some antiatherosclerotic effect not dependent on blood pressure reduction. In that connection, it is worth considering those effects of antihypertensive drugs which may impact on atherosclerosis.

Curiously, about the same time as evidence has finally become available to support the hypothesis that treatment to lower blood cholesterol levels is effective in reducing risk of myocardial infarction,¹³ there has been increasing awareness that antihypertensive drugs have adverse effects on lipoproteins. Whereas the Lipid Clinics Coronary Prevention Trial showed that an average reduction of cholesterol by 9% reduced coronary risk by 20%,¹³ it has recently become apparent that thiazide diuretics and nonselective beta-blockers have, on average, about a 15% adverse effect on triglycerides and cholesterol/HDL ratio.^{5,14–20} Ames²¹ and Woodcock and Rietbrock²² have calculated that the adverse effects of such drugs on lipoproteins is enough to completely offset the benefit of treating mild hypertension. Since most patients with hypertension are mildly hypertensive,²³ this issue assumes great importance.

Two strategies are apparent for solving the problem of the adverse effects of antihypertensive drugs on lipoproteins: firstly, to search out drugs which lower

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blood pressure and improve lipoproteins; secondly, to continue using drugs which are in conventional use, and to seek out ways to offset their adverse effects. A recent attempt at the second strategy, by using amiloride and salbutamol to offset the adverse effect of thiazide and beta-blocker was not effective,²⁴ suggesting that the first strategy of seeking out better drugs, may be more useful.

Another effect of antihypertensive drugs that appears to affect atherosclerosis has to do with the hemodynamic effects that affect arterial flow disturbances such as turbulence. Although biophysicists argue about the relative importance of high shear, low shear, boundary layer impingement, axial stream impingement, and other departures from laminar flow that may lead to endothelial damage, it is apparent that all such disturbances of flow pattern occur under the same hemodynamic conditions,²⁵ so that in order to develop an approach to the prevention of their occurrence, it is not necessary to settle the argument about which is most important.

We first proposed in 1974 that antihypertensive drugs which diminish the occurrence of arterial flow disturbances may be more effective in preventing atherosclerosis, than drugs which do not.²⁶ Since then, we have shown in monkeys and in hypertensive patients that antihypertensive drugs have different effects on blood velocity,^{27, 28} that a beta-blocker, propranolol, diminishes while hydralazine, a vasodilator, increases the occurrence of abnormal high-velocity patterns such as turbulence and vortex formation in patients with carotid stenosis,²⁹ and that propranolol was significantly more effective than hydralazine in preventing aortic atherosclerosis in a cholesterol-fed rabbit model. Others have recently shown that verapamil was antiatherosclerotic in a rabbit model,³⁰ that propranolol decreases aortic endothelial turnover,³¹ and that propranolol but not hydralazine prevents atherosclerosis in broad-breasted turkeys.³² There has been some suggestion that the beneficial effects of propranolol may be on a metabolic rather than a hemodynamic basis.^{31, 33, 34} The most exciting work to date is the work of Kaplan et al, at Winston-Salem, who showed that metoprolol, a beta-blocker, reduced coronary atherosclerosis by 50% in the dominant males of the socially unstable groups, in a monkey model.³⁵ In this model, in which the animals are not hypertensive, the beta-blocker appears to offset the effects of stress.

These discrepancies are confusing to those who are accustomed to thinking of hypertension only in terms of pressure. Burton's treatment of the Bernoulli principle³⁶ illustrates that although under conditions of laminar flow most of the fluid energy is in the form of pressure energy, there is conversion of pressure energy to kinetic energy whenever flow becomes non-laminar. Thus, drugs which cause the appearance of turbulence and other departures from laminar flow at stenoses and bifurcations will result in the conversion of pressure energy to kinetic energy, which is transmitted to the vessel wall, and has the potential to lead to endothelial damage, and to the consequent reaction to

injury which is thought to be the pathogenesis of atherosclerosis.³⁷⁻⁴⁰

The problem of antihypertensive drugs and atherosclerosis is increasingly important, now that strokes due to hypertensive small vessel disease are coming under control. At present studies are under way to evaluate the effects of beta blockers on the rate of progression of carotid stenosis; it is to be hoped that any new major studies of antihypertensive treatment will take into account the effects of drugs not only on pressure, but also on those physiological effects that may affect atherosclerosis and its complications.

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