batch processed at the end of the day; patients with values above $0.1 \mu g \cdot 1^{-1}$ constitute a high-risk group$^{[10]}$ who should be admitted. In usual hospital practice, it would be convenient to keep the patients with normal admission values overnight, so that they can be assessed at a time adjacent to the cardiac care unit round on the following morning, at which time all marker values measured between admission and $12$ h following admission should be available. Patients who have values below $0.1 \mu g \cdot 1^{-1}$ on every occasion, and in whom there is no clinical feature of concern, could then be discharged for outpatient exercise testing and clinical assessment.

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References


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**Can calcium antagonists reverse atherosclerosis?**

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There is little doubt that calcium antagonists are effective in treating the symptoms of angina pectoris. Although there are concerns that short acting calcium antagonists may adversely affect mortality in angina pectoris, long acting antagonists have not been so implicated. For example, Lichtlen et al. (see the CAPE study in the supplement to this volume) showed no evidence of amlodipine triggering arrhythmias in patients with stable angina and proven periods of silent ischaemia$^{[11]}$. In the accompanying issue of the *European Heart Journal Supplement* the current state of knowledge as regards calcium antagonists in general, and amlodipine in particular, is described in terms of the effect on morbidity. But perhaps the key issue — and it has been around for some years — is whether calcium antagonists can slow down or reverse the structural changes of atherosclerosis. Thirteen years ago, Fleckenstein was proposing an ‘arterial anticalcinotic’ effect of calcium antagonists$^{[2]}$, and the jury is still out.

Two early studies with dihydropyridines (the INTACT Study 1990; Waters et al., 1990) showed that these calcium antagonists had little effect in advanced coronary disease, but could reverse early lesions$^{[3,4]}$. The INTACT study tested nifedipine against placebo for 3 years; there was a 28% reduction in the number of new lesions per patient ($P<0.03$). In the study by Waters et al., nicardipine (another short-acting calcium antagonist) was tested against placebo, and coronary angiography was repeated after 2 years. Advanced lesions did not differ in the two groups, but there was a reduction in the progression of small or new lesions from 27 to 15%
Waters et al. asked the important question of whether the effects were secondary to a fall in blood pressure, and did in fact show a correlation between blood pressure reduction and the occurrence of new lesions. It was not possible to identify such a relationship in the INTACT study. Previously Loaldi et al. (1989) had compared the effect of nifedipine, propranolol and isosorbide on coronary angiography after 2 years of treatment. This study was less robust statistically than the two previously described. Regression of lesions was significantly commoner in patients taking nifedipine, even though the fall in blood pressure was indistinguishable in the three groups. It would be of great interest to repeat Loaldi et al.’s study using more patients, and a longer-acting beta-blocker and calcium antagonist.

Since these studies were done, a new generation of atherosclerosis trials has appeared involving measurement of carotid wall thickness, rather than direct measurement of coronary arteries. Use of B-mode quantitative ultrasound on the carotids has the great advantage of non-invasiveness, but the potential disadvantage of being a surrogate measurement. (It is assumed that atheromatous change in the wall of the carotid mirrors changes in the coronary vessels, even though anatomically they are very different types of arteries.) An early carotid study (SHEP) did not use B-mode ultrasound, but serial carotid duplex scans that could only examine stenoses that were >40–50% of the lumen diameter. But, in spite of these disadvantages the study showed that lowering blood pressure using placebo-controlled chlorthalidone ± atenolol significantly lessened progression and increased regression of carotid stenoses. The use of B-mode quantitative ultrasound has been demonstrated in MIDAS, an ambitious examination of 12 sites in the common carotid, in which the mean maximum intimal-medial thickness was measured. Eight hundred and eighty-three hypertensive patients were randomized to isradipine or chlorthalidone. At 6 months, in spite of the diuretic-treated patients having a greater systolic blood pressure reduction, the increase in thickness was four times greater in the diuretic group. This did indeed suggest that the calcium antagonist was having an anti-atherosclerotic effect. Oddly, the 6 month difference persisted unchanged throughout the 36 month follow up period.

Measurement of the mean maximum intimal-medial thickness is useful, but it has a certain ambiguity. For in atherosclerotic carotids it includes both smooth muscle (hypertrophy) and the more amorphous changes of atherosclerosis. From what we have seen so far, it is possible that calcium antagonists might reduce the muscle hypertrophy, but are less likely to reduce the sclerotic changes: unfortunately the ultrasound cannot help us with these alternatives.

Animal models of atherosclerosis (for example, the production of plaques in rabbits by feeding high cholesterol diets) can be shown to be completely reversible with calcium antagonists — an observation that gave false hope to earlier studies of human coronary artery disease with calcium antagonists. Reversible plaques in animal models do not show the fibrosis and other histological features seen in human plaques. Since calcium antagonists are capable of reversing the early stages of arteriosclerosis, there must be some threshold point beyond which the changes are irreversible. Could it be that the calcium antagonists just cannot enter the plaque?

Lipid lowering drugs such as statins can cause shrinkage and even disappearance of plaques. The mature plaque contains very much more lipoprotein than calcium, and the lipoprotein is presumably in some sort of equilibrium with plasma lipids. Lowering of plasma lipids by statins could result in diffusion of lipoprotein down a concentration gradient — there obviously cannot be an analogous process with calcium. If calcium antagonists were to have any calcium-removing effect on the mature plaque, they would need to penetrate this fatty substance; calcium antagonists are not this lipophilic, with the possible exception of an unusual molecule, lacidipine.

Lacidipine, a long-acting calcium antagonist, is licensed for use in hypertension. It is characterized by a very high membrane partition coefficient compared with other dihydropyridines. Its lipophilic nature, and the prolonged time that it spends within cell membranes, has led to hopes that lacidipine may have an exceptional anti-atherosclerotic action. This is being tested in an ongoing study, ELSA (European Lacidipine Study on Atherosclerosis). This is a 4-year trial in 2300 hypertensive patients comparing the effect of lacidipine with atenolol on carotid wall thickness. A second ongoing lacidipine study, SHELL (Systolic Hypertension in the Elderly Long-term Lacidipine trial) involves 4800 patients aged over 70 years, but is not looking primarily at the drug’s effects on atherosclerosis.

The world has indeed high hopes for calcium antagonists in atherosclerosis. Van Zwieten (1998) in a recent survey lists no less than 15 ongoing substantial trials involving calcium antagonists, and the results of most of these will hinge on the anti-atherosclerosis effects. All involve long-acting calcium antagonists (five involving amlodipine, two lacidipine (see above), two verapamil, one diltiazem, one felodipine, one irbesartan, one nifedipine-GITs and two various calcium antagonists). If early work
involving short acting calcium antagonists is borne out, and early lesions are the only reversible ones, we might expect only patients with the lowest levels of hypertension and the lowest baseline atheroma to respond. But the enthusiasm for setting up these trials suggests a faith that long-acting calcium antagonists can somehow achieve more than this. Let us hope this faith is justified.

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References


Controversies in determining cardiovascular therapy

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In recent years, there have been major advances in our understanding of the epidemiology and treatment of coronary heart disease. We now have the knowledge base and tools to implement a major reduction in cardiovascular morbidity and mortality. For example, it is well known that risk factor modification, in particular lipid lowering, is effective in reducing coronary heart disease. Results of several large-scale secondary and primary prevention studies have left little doubt as to the effectiveness of HMG-CoA reductase inhibitors (statins) in producing beneficial lipid-lowering in individuals at risk of coronary heart disease. Statins have been shown to reduce significantly cardiovascular morbidity and mortality and are well tolerated.

Despite this compelling evidence, data from several parts of the world indicate that physicians, including cardiologists, are not utilizing optimal lipid management in clinical practice. Even in patients at high risk of coronary heart disease, such as those with multiple risk factors and those undergoing revascularization, the use of statin therapy is low. Coronary heart disease, therefore, remains the leading cause of mortality in the Western world.

Many questions remain regarding lipid-lowering therapy, including:

- What is the optimum low density lipoprotein cholesterol target level in patients at risk of coronary heart disease?