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The Effect of Pravastatin on Intima Media Thickness of the Carotid Artery in Patients with Normal Cholesterol

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Objective. *Carotid intima media thickness (IMT) is a good indicator of the severity of atherosclerotic disease. Statins have been found to reduce carotid IMT in patients with hypercholesterolaemia. The aim of this study was to investigate if pravastatin is effective in reducing IMT in normocholesterolaemic patients with carotid artery disease.*
Methods. *Patients with carotid artery stenosis and normal cholesterol levels who were not on a statin, were recruited. Patients were randomised to receive pravastatin or placebo daily. Serum concentration of cholesterol and IMT of common carotid arteries were measured before randomisation and at 3 monthly intervals thereafter, for 9 months. IMT was analysed to give the mean of a standardised 2 cm of the common carotid artery (CCA). Results are expressed as median (IQR) and comparison made using the Wilcoxon signed ranks test.*
Results. *Fifty-four patients were examined. Twenty-eight patients were randomised to active treatment. There was no difference in demographic details and co-morbid states between the two groups. A significant reduction in cholesterol concentration was observed from 3 months in patients randomised to the pravastatin group [5.14(4.72–5.88)* vs. *4.11(3.44–5.33),* $p < 0.05$*], while there was also a significant decrease in combined IMT form 6 months [1.53(1.36–1.87)* vs. *1.41 (1.33–1.78),* $p < 0.05$*].*
Conclusions. *The results demonstrate that pravastatin reduces intima media thickness of the common carotid artery in normocholesterolaemic patients with moderate carotid stenosis.*

Keywords: Intima media thickness; Carotid artery; Normal cholesterol.

Introduction

Various non-invasive markers of early arterial wall alteration are currently available, such as arterial wall thickening and stiffening, endothelial dysfunction and coronary artery calcification.[1] Intima media thickness (IMT) of the common carotid artery was recommended as a useful parameter to assess the presence of coronary artery disease in a recent publication of the American Heart Association.[2] IMT is the combined thickness of the arterial intima and media as measured on B-mode ultrasound. It is a relatively simple procedure, and represents a safe, inexpensive, precise and reproducible measure.[3]

In observational and epidemiological studies, a relationship has been found between IMT and a number of cardiovascular risk factors such as male sex, ageing, obesity,[4] hypertension,[5,6] hypercholesterolaemia,[7,8] diabetes[9,10] and cigarette smoking.[11,12] Several prospective studies of asymptomatic subjects in primary prevention have tested the predictive value of IMT with regard to clinical cardiovascular complications[13–18] such as myocardial infarction or stroke. All these studies are concordant in demonstrating that increased IMT is a powerful predictor of coronary and cerebrovascular complications. The quantitative value, reproducibility and high precision of carotid IMT measurement means it is more and more frequently used in therapeutic trials to test the effects of drugs.

Various trials have demonstrated that lipid-lowering drugs, statins, can significantly decrease IMT progression in patients with hypercholesterolaemia.[19–23] The aim of this study was to investigate whether pravastatin decreased IMT in patients with normal pre-treatment cholesterol concentrations.

Methods

This study was approved by the local Research Ethics Committee.

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Study population

All patients with carotid artery disease referred to the Vascular Surgery Unit of Belfast City Hospital between August 2001 and February 2003 were considered. Carotid duplex was carried out by one of two trained technicians to confirm the severity of stenosis and random cholesterol was measured. Patients with carotid artery disease who were not undergoing surgery and had cholesterol concentration less than 5.5 mmol/l were included. Patients were excluded if they were already on a cholesterol-lowering drug or had previous carotid endarterectomy. Written informed consent was obtained and demographic details, relevant history, risk factors for vascular disease, and current medications were recorded.

Randomisation

Patients were randomly assigned in blocks of four in a blinded fashion to receive treatment with either pravastatin 40 mg daily or placebo. The statin medication was initiated and maintained at the target study dose throughout the duration of the study. All patients who completed the study demonstrated compliance with the treatment program through return visits for prescription refills and clinic visits for laboratory analysis. Compliance was enhanced through central control of study medication and prescriptions and mailed reminders for the timing of study-related procedures.

Carotid B-mode ultrasound

An ATL5000 duplex ultrasound scanner with L4-7 MHz linear array transducer was used to image both sides of the neck of each subject. One operator, blinded to patient treatment or randomisation performed all the scans. The subjects were asked to lie supine on a couch. The carotid artery bifurcation was located as a reference point and then a high resolution, high-density longitudinal B-mode image of the CCA just before the bifurcation was visualised. This represented images showing 2 cm lengths of the distal common carotid artery. In all cases, an attempt was made to keep the far wall of the artery parallel with the scanner head so as to enable a high quality, best resolution image of the intima and media features of the artery wall. Images were recorded at each visit and for each side of the neck. These images were transferred in a digital format to a PC to be stored and analysed off-line. The transferred images were composed of the raw data and retained the original spatial resolution. They also allowed adjustment of brightness and contrast.

The stored images for each subject were analysed at the end of the study so that each set of images from the same side of the neck could be compared for the different visits. Images were rejected if there was extensive plaque formation throughout the length of the vessel or if there was poor repeatability.

The 'HDILab' research program, with computer edge tracking software, was used to measure the intima-medial thickness (IMT). The edge tracking software was employed over a 10 mm length of the far wall of the vessel normally extending over the region from 1 to 2 cm below the bifurcation. If there were small areas of plaque formation these were avoided or omitted from the measurement when possible. The ability of the edge tracking software to locate the edge of the intima and media was monitored visually and when necessary was adjusted manually. The average thickness and standard deviation along this 10 mm length was recorded for each image (Fig. 1).

Baseline measurements were recorded for each subject before treatment/randomisation. Patients were reviewed at 3-monthly intervals until termination of the study. At each follow-up visit, IMT was measured and a blood sample taken to measure random cholesterol concentration.

Statistical analysis

The calculation of sample size was based on the estimated change in IMT. It was assumed that the rate of progression of IMT was 0.2 mm/year $\pm$ 0.12 (estimated on a 3 year follow-up). It was calculated that 80 patients would be required to achieve 90% power with significance of 5% after a treatment period of 9 months.

Demographic details were analysed using the χ^2 test. The changes from baseline of combined IMT of right and left CCAs were analysed using non-parametric tests. Data are presented as median (IQR). As multiple comparisons were made, a Bonferroni correction was applied which altered the p value at which statistical significance was achieved to 0.017. All statistical analysis was performed using SPSS software (version 10, SPSS Inc., Chicago).

Results

Fifty-four patients were recruited and twenty-eight randomised to active treatment. There was no significant difference between the major demographic

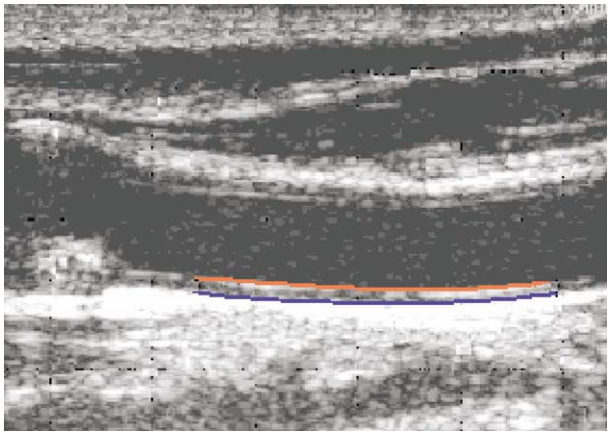

Fig. 1. Image showing edge tracking software to identify lumen: intima and media: adventitia interfaces.

features or cardiovascular risk factors between the two groups (Table 1). There was no significant difference between groups in the use of other cardiovascular medication including beta-blockers, calcium channel blockers, aspirin and angiotensin converting enzyme inhibitors either at the beginning or end of the study.

Primary and secondary endpoints

Table 2 shows the serological measurements of cholesterol concentration at various time points for the two experimental groups. There was no significant difference at baseline between placebo and pravastatin groups in total cholesterol concentration [5.39(4.72–5.88) *vs.* 5.14(4.77–5.91), $p=0.7$] but as expected there was a significant decrease from baseline measurement in the pravastatin group compared to placebo at 3, 6, and 9 months following randomisation.

IMT was analysed as the combined IMT of the right and left CCAs. There was again no significant difference at baseline between placebo and pravastatin groups [1.52(1.28–1.68) *vs.* 1.53(1.36–1.87), $p=0.5$]. There was a reduction in intima thickness in the pravastatin group compared to the placebo group, which was significant at 3 months ($p=0.016$), 6 months ($p=0.011$) and 9 months ($p=0.01$) following randomisation (Table 3). No correlation was demonstrated between the changes in cholesterol concentration and IMT in the pravastatin groups of patients ($r=-0.18$).

Table 1. Clinical risk factors for non-surgical patients randomised to pravastatin or placebo

Risk factor	Placebo ($n=26$)	Pravastatin ($n=28$)	p value
Age, mean (SEM), year	70(1.5)	71(1.3)	0.77
Sex, male:female	24:9	23:8	0.89
Smoking, n(%)	18(55)	17(55)	0.98
IHD, n(%)	6(18)	7(23)	0.90
Diabetes, n(%)	4(12)	5(16)	0.92

Smoking, past or present history of smoking; IHD, ischaemic heart disease, past history of myocardial infarction or angina requiring treatment; diabetes, insulin and non-insulin dependent requiring treatment, including diet controlled.

Table 2. Cholesterol (mmol/l) concentration at 3, 6 and 9 months following randomisation

	Baseline	3 Months*	6 Months*	9 Months*
Pravastatin ($n=28$)	5.14 (4.72–5.88)	4.11 (3.44–5.33)	4.21 (3.67–4.85)	4.21 (3.38–5.19)
Placebo ($n=26$)	5.39 (4.72–5.88)	5.03 (4.30–6.04)	5.35 (4.54–5.96)	5.16 (4.67–5.91)

* Significant difference in change from baseline between placebo and pravastatin groups.

Discussion

Atherosclerosis is a dynamic process characterised by vessel wall remodelling that develops over decades, ultimately manifesting as acute cardiovascular events in many individuals.[24] Epidemiologic and interventional studies using cardiovascular clinical endpoints require long study periods and large populations to establish the influence of risk factors and effects of therapeutic interventions in preventing such disease outcomes. B mode ultrasonographic imaging permits non-invasive real-time high resolution imaging of superficial artery walls, thus, allowing visualisation of the effects of the atherosclerotic process.

Several observational studies have shown that individuals with cardiovascular disease have greater IMT values. The latter has been shown to be associated with increased risk of clinical symptoms.[14,17,25] The effects of statin therapy on atherosclerosis have been assessed by high-resolution ultrasonographic measurement of carotid IMT in a number of studies. However, the lack of a standardised protocol for measuring IMT change makes inter-study comparison difficult. In particular, imaging protocols vary with respect to the carotid artery selected for measurement, i.e. right or left CCA, the carotid bulb or internal carotid artery, as well as the specific segment of the

Table 3. Combined IMT(mm) at 3, 6 and 9 months following randomisation

	Baseline	3 Months	6 Months*	9 Months*
Pravastatin ($n=28$)	1.53 (1.36–1.87)	1.54 (1.31–1.85)	1.44 (1.33–1.78)	1.37 (1.30–1.68)
Placebo ($n=26$)	1.52 (1.28–1.68)	1.50 (1.31–1.71)	1.54 (1.32–1.75)	1.47 (1.23–1.84)

* Significant difference in change from baseline between placebo and pravastatin groups.

artery. In this study, both CCAs were analysed, and an image was taken of the carotid bifurcation at baseline so that this constant point could be used as a reference and the IMT measured over an identical segment of the artery at subsequent visits. The IMT was calculated using a computer program removing any observer bias. It was felt that this was the most accurate method of measuring IMT and the results were, therefore, reliable as shown by the small interscan variability of less than 5%.

This double-blinded randomised trial demonstrated regression of IMT within 6 months and marked cholesterol reduction in normocholesterolaemic patients with pravastatin 40 mg compared to placebo. These results corroborate with those in previous studies, which have found a significant decrease in IMT in patients on a statin over a relatively short period of time. In contrast to this study others investigated the effect of statins in hypercholesterolaemic patients. The REGRESS study[21] showed that pravastatin had an effect on both the carotid and femoral artery walls in patients with angiographic coronary artery disease and total cholesterol levels ranging from 4 to 8 mmol/l. The results were presented as a combined IMT of the carotid and femoral arteries. The ASAP trial[26] compared the effects of simvastatin and atorvastatin in patients with familial hypercholesterolaemia. This trial combined common and internal carotid artery thickness as an outcome measure and found that atorvastatin significantly decreased IMT. The ARBITER study[27] investigated patients with elevated cholesterol levels but found that there was enhanced benefit with more aggressive lipid lowering even below recommended guidelines. In this study, we investigated patients with low to normal pre-treatment cholesterol levels and differed from previous investigations in that the patient population had carotid artery disease rather than coronary artery disease with or hypercholesterolaemia. This limited our measurement of IMT due to the presence of severe atherosclerotic involvement of the ICA in the majority of patients.

A reduction in IMT was evident as early as 6 months after starting treatment. It seems unlikely that plaque regression can be related to the lipid lowering properties of pravastatin after such a short period. However, pravastatin may exert its antiatherogenic role by directly affecting the rate of lipid deposition in macrophages in the atherosclerotic plaque,[28] as well as by improving defective endothelium-dependent vasodilatation[29,30] and reducing platelet thrombus formation in flowing blood.[31] This hypothesis is reinforced by the lack of correlation between the change in IMT and cholesterol concentration ($r = -0.18$).

One major limitation of this study is the small sample size due to the untimely publication of the MRC/BHF Heart Protection Study in 2002.[32] This resulted in many patients with normal cholesterol levels being prescribed statin by their general practitioner or referring physician before attending the vascular unit for assessment of their carotid disease.

In conclusion, the effect of pravastatin treatment on carotid IMT progression is beneficial even in normocholesterolaemic patients. However, the cholesterol-lowering effect of pravastatin does not entirely explain the reduction in IMT. Further placebo-controlled randomised trial in the future will be difficult due to the recent publication of the Heart Protection Study, which provides convincing evidence that statins are beneficial to all patients with risk factors for cardiovascular disease regardless of initial cholesterol concentration.

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