Managing hypercholesterolemia and its correlation with carotid plaque morphology in patients undergoing carotid endarterectomy

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Purpose: Hypercholesterolemia is a critical problem in patients with carotid atherosclerosis. The adequacy of attention to lipid risk factors in patients with carotid stenosis awaiting carotid endarterectomy (CEA) has rarely been studied. We also assessed patient awareness of hypercholesterolemia and carotid plaque morphology.

Methods: A prospective study was conducted of 141 consecutive patients admitted electively for CEA. Each patient's medical history was taken. Plasma cholesterol concentrations were determined. Plaque histology was scored according to American Heart Association criteria and their modification.

Results: Of patients who were aware of their hypercholesterolemia and who were receiving treatment, 28.6% had total cholesterol levels ≥5 mmol/L. Among those patients who had been told that they had no problem with hypercholesterolemia, 32.5% had plasma cholesterol concentrations ≥5 mmol/L. Among those patients who had never had their plasma cholesterol measured, 48.4% had total cholesterol levels ≥5 mmol/L. Patients in this last group tended to have more severe types of plaque pathology than those in other groups (12.9% plaque rupture).

Conclusions: Hypercholesterolemia does not seem to be well managed in patients awaiting CEA.

Keywords: cholesterol, carotid endarterectomy, hypercholesterolemia, atherosclerotic plaque

Introduction

Hypercholesterolemia is one of the most important risk factors in the development and progression of atherosclerosis, the major cause of vascular disease (Castelli 1984). Hypercholesterolemia has also been reported to be associated with myocardial infarction (Kannel et al 1971). It can be modified by diet or drugs. Indeed a number of randomized controlled trials (RCTs) of lipid-lowering medications (both primary and secondary prevention) have shown clear clinical benefit of the effects on cardiovascular events (Shepherd et al 1995; Sacks et al 1996; HPS 2002). This benefit has been shown in both short and long term results. The West of Scotland Coronary Prevention Study (WOSCOPS) was an RCT comparing pravastatin with placebo in men with hypercholesterolemia, and no history of myocardial infarction, with an average follow-up of approximately 5 years (Barringer 1997). The combined outcome of death from definite coronary heart disease or definite nonfatal myocardial infarction was reduced from 7.9% in the control group to 5.5% ($p < 0.001$) in the pravastatin group (Ford et al 2007). In the 10-year follow-up after this RCT was completed, 38.7% of the original statin group and 35.2% of the original placebo group were being treated with a statin. The risk of death from coronary heart disease or nonfatal myocardial infarction was 10.3% in the placebo group and 8.6% in the pravastatin group ($p = 0.02$) (Ford et al 2007).

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Many protocols and guidelines have therefore stressed the importance of detection and control of hyperlipidemia, especially hypercholesterolemia, in patients with atherosclerosis (JBS1 1998; NCEP 2001; Stroke Council 2004; Grundy et al 2004). Patients with coronary artery disease (CAD) are likely to have their hypercholesterolemia treated, but many studies have found that physicians still do not fully acknowledge the importance of treating hypercholesterolemia in all patients with atherosclerosis (Cohen et al 1991; Rajagopalan et al 2007).

The Heart Protection Study, a large RCT, compared the 5-year risk of vascular events in patients with a high risk of coronary death receiving either simvastatin or placebo (HPS 2002). In a study subgroup, patients with cerebrovascular disease who were taking statins, including those who had undergone carotid endarterectomy (CEA), also had a significantly lower risk of major vascular events (combined rate of coronary events, strokes and re-vascularizations 24.7%) than those in the control group (29.8%). Similarly, recent trials in patients with recent stroke or TIA and no known coronary heart disease showed that 80 mg of atorvastatin per day reduced the overall incidence of strokes and cardiovascular events (Amarenco et al 2006). These results indicate that patients for whom CEA is indicated, should survive longer or have less chance of major vascular events if their hypercholesterolemia is managed properly. Moreover there is compelling evidence that hypercholesterolemia is a risk factor for carotid re-stenosis after CEA (Das et al 1985; Rapp et al 1987).

Despite the overwhelming evidence of the risk of hypercholesterolemia in patients with peripheral vascular disease, including carotid artery stenosis (CAS), to our knowledge no study has examined the management of hyperlipidemia and carotid plaque morphology. The first objective of this study was to examine the incidence of hypercholesterolemia among patients awaiting CEA and to relate this incidence to patient awareness of their hypercholesterolemia. A second objective was to study the relationship of patient awareness of hypercholesterolemia and carotid plaque characteristics determined by morphological examination.

Methods

The study was approved by our Research Ethics Committee, and written informed consent was obtained from the patients recruited. From 1998 to 2001, 141 consecutive patients were included prospectively. Medical histories were taken, including patient awareness of hypercholesterolemia. Patient records including drug charts were checked for use of any lipid-lowering medication. On the pre-operative visit, fasting venous blood samples were taken and stored in vacutainer tubes containing 0.12 mL of 15% EDTA. Plasma was prepared by centrifugation at 1500 g for 10 minutes and stored at –80 ºC. Concentrations of total plasma cholesterol were determined using a commercially available, enzyme-based diagnostic kit.

The carotid plaques removed at surgery were cleaned with saline. Serial transverse 2 mm sections were taken. These sections were labeled alphabetically starting from the distal end of the internal carotid artery and ending at the common carotid artery. Paraffin-embedded sections were stained with hemoxylin and eosin. The section closest to the bifurcation was classified according to the guidelines published by the American Heart Association (AHA) system (the Stary system) (Stary et al 1995), and a proposed modification of this system (Virmani et al 2000).

Analysis

Patient awareness of hypercholesterolemia was classified in three ways. Group 1 patients were those who were aware of an abnormality and who had been given treatment or advice. Group 2 patients claimed that their doctors had said that their blood tests were normal. Group 3 patients were unaware of any testing of blood lipids. At the time of this study the AHA guidelines recommended that for patients with major atherosclerotic disease, including patients who had undergone CEA, plasma total cholesterol should be less than 5 mmol/L (JBS1 1998). Patients in the three groups were classified into two further sub-groups: those with plasma cholesterol concentrations greater than or equal to 5 mmol/L and those with plasma cholesterol concentrations less than 5 mmol/L. These three groups were also classified by carotid plaque pathology according to AHA and modified AHA score. All data are described in percentages. The comparison between groups was determined by chi-squared test. $P < 0.05$ was considered to indicate statistical significance.

Results

Eighty-one males and 60 females with a mean age of 69.4 years were included; 41.1% of these patients had a history of either angina or myocardial infarction and 9.2% had previously undergone contralateral CEA. The mean blood pressure and the percentage of current smokers were higher in Group 3 than in the other two groups (Table 1). In Group 1, 53% of patients were on statin medication, with a median duration of 3.5 years.

Table 1 Patient characteristics at study entry

	Group 1 N = 70	Group 2 N = 40	Group 3 N = 31
Gender: men (%)	37 (52.9)	22 (55.0)	22 (71.0)
Mean age (years, mean (SD))	68.4 (7.7)	73.1 (8.3)	70.3 (9.0)
Body mass index (kg/m^2, mean (SD))	26.7 (4.2)	25.6 (3.3)	25.8 (3.9)
Clinical history (%)			
Hypertension	57 (81.4)	23 (57.5)	23 (74.2)
Diabetes	18 (25.7)	6 (15.0)	8 (25.8)
Angina pectoralis	12 (17.1)	4 (10.0)	5 (16.1)
Myocardial infarction	10 (14.3)	2 (5.0)	4 (12.9)
Smoking status (%)			
Current smokers	8 (11.4)	5 (12.5)	5 (16.1)
Ex-smokers	51 (72.9)	26 (65.0)	19 (61.3)
Mean arterial blood pressure (mmHg, mean (SD))			
Systolic	161.1 (24.5)	163.3 (26.6)	167.3 (25.9)
Diastolic	84.5 (14.3)	85.9 (15.0)	87.5 (13.3)
Drug use (%)			
Aspirin	70 (100.0)	40 (100.0)	31 (100.0)
Beta-blocker	16 (22.9)	9 (22.5)	8 (25.8)
ACE inhibitor	14 (20.0)	8 (20.0)	7 (22.6)
Nitrates	12 (17.1)	7 (17.5)	6 (19.4)
Calcium channel blocker	25 (35.7)	14 (35.0)	11 (35.5)
Fibrates	2 (2.9)	0	0
Statin	37 (52.9)	0	0
Insulin	4 (5.7)	2 (5.0)	2 (6.5)
Oral antidiabetics	8 (11.4)	5 (12.5)	4 (12.9)

Notes: Group 1 patients were those who were aware of an abnormality and had been given treatment or advice. Group 2 patients claimed that their doctors had said that their blood tests were normal. Group 3 patients were unaware of any previous testing of blood lipids.
Abbreviations: ACE, angiotensin converting enzyme; N, total; SD, standard deviation.

Of 141 patients (34.0%) awaiting carotid endarterectomy, 48 had levels of total cholesterol greater than or equal to 5 mmol/L (Table 2). Because their physician had informed them of it, 70 patients were aware of their hypercholesterolemia (Group 1). Twenty of these 70 patients (28.6%) still had total cholesterol levels greater than this. Interestingly, in Group 1, 33 patients had histories of ischemic heart disease and nine patients (12.9%) in this subgroup still had total cholesterol levels greater than 5 mmol/L. Because their physicians had informed them that they did not have hypercholesterolemia, 40 patients denied having this condition (Group 2); 13 patients in this group (32.5%) had levels of total cholesterol ≥5 mmol/L. Thirty-one of 141 patients (22%) had never had their cholesterol levels checked or were unaware of any previous cholesterol tests (Group 3). Fifteen patients in this group (48.4%) had total cholesterol levels ≥5.0 mmol/L.

Carotid plaque morphology in Group 3 tended to be more severe (according to AHA classification) than in the other groups (Table 3). The combined percentages of Type V and

Table 2 The relationship between plasma total cholesterol concentration (≥5 mmol/L versus <5 mmol/L) and the awareness of patient of hypercholesterolemia (n (%))

Plasma cholesterol	Group 1 N = 70	Group 2 N = 40	Group 3 N = 31	p value
≥5 mmol/L	20 (28.6)	13 (32.5)	15 (48.4)	0.148
<5 mmol/L	50 (71.4)	27 (67.5)	16 (51.6)	

Abbreviation: N, total.

Table 3 Relationship between patient awareness of hypercholesterolemia and carotid plaque morphology (% of patients)

	Group 1 N = 70	Group 2 N = 40	Group 3 N = 31	p value
AHA classification type				
III	0	0	3.2	0.371
IV	64.3	75.0	54.8	
Va	21.4	17.5	22.6	
Vb	4.3	5.0	3.2	
VI	10.0	2.5	16.1	
Modified AHA classification type				
Pathological intimal thickening	8.6	2.5	6.5	0.367
Fibrous cap atheroma	58.6	72.5	51.6	
Thin fibrous cap atheroma	22.9	17.5	25.8	
Erosion	1.4	2.5	0	
Plaque rupture	4.3	0	12.9	

Abbreviations: AHA, American Heart Association; N, total.

VI in Groups 1, 2, and 3 were 35.7%, 25.0%, and 41.9% respectively. Similarly patients in Group 3 had a higher percentage of plaque rupture than the other groups. Patients with plasma cholesterol ≥5 mmol/L tended to have a higher grade of plaque morphology than those with lower plasma cholesterol (Table 4). However these trends did not reach statistical significance. There was no statistically significant perioperative complication after CEA among three groups (Table 5).

Discussion

Despite overwhelming evidence demonstrating the benefits of lipid lowering therapies in vascular patients, in clinical practice hyperlipidemia is poorly managed (Aspry et al 1995). Mismanagement is evident in the current study, because 22% of these patients had apparently never had their lipid profiles checked or were unaware of any previous plasma lipid tests. Similarly, Burns and colleagues found that 47% of patients with peripheral arterial disease had never had a cholesterol measurement (Burns et al 2002). Perhaps even more disappointingly, around one third of patients who had been treated for hypercholesterolemia (Group 1) still had total cholesterol levels higher than the recommended level (≥5 mmol/L). Similarly, a cross-sectional analysis by Rajagopalan et al of 70,194 UK patients who had begun lipid modifying therapy in 2005, found that 21.8% of patients with evidence of atherosclerosis had plasma

Table 4 Relationship between plasma cholesterol and carotid plaque morphology (% of patients)

	Cholesterol level ≥5 mmol/L N = 48	Cholesterol level <5 mmol/L N = 93	p value
AHA classification type			
III	0	1.1	0.596
IV	58.3	68.6	
Va	22.9	19.4	
Vb	6.3	3.2	
VI	12.5	7.5	
Modified AHA classification type			
Pathological intimal thickening	8.3	5.4	0.577
Fibrous cap atheroma	50.0	66.7	
Thin fibrous cap atheroma	25.0	20.4	
Erosion	2.1	1.1	
Plaque rupture	8.3	3.2	

Abbreviations: AHA, American Heart Association; N, total.

Table 5 Peri-operative complications following carotid endarterectomy (%)

Postoperative complication	Group 1	Group 2	Group 3
Myocardial infarction	1 (1.5)	0	0
Stroke	2 (2.9)	1 (2.6)	1 (3.4)
Death	1 (1.5%)	0	0

cholesterol ≥5 mmol/L. This result is comparable with the data from Group 1 in our study.

There were several possible impediments to the guidelines (JBS1 1998). Many physicians did not want to follow the guidelines partly due to knowledge deficiency or a negative attitude toward the guidelines (Frolkis et al 1998). Also many general practitioners reported that their concern about patient ability to understand and adhere to treatment recommendations, increased workloads, and medication costs (Kedward and Dakin 2003). Another reason for this ignorance is that some clinicians believe that once a patient has severe carotid stenosis and is waiting for carotid surgery, lipid-lowering drugs are no longer beneficial. In other words, it is already too late to treat a severely stenotic lesion. While it is true that a severely stenotic lesion is unlikely to regress in the short term, in many trials statins have reduced the incidence of myocardial infarction (Ford et al 2007), the main cause of death peri-operatively and long-term after CEA (Musser et al 1994; Kerdiles et al 1997). Nevertheless, this effect was not demonstrated (Table 5) in our study perhaps because of the small sample size.

To achieve a high long-term survival rate for patients undergoing CEA, adequate management of hypercholesterolemia is of paramount important because myocardial infarction is the most common cause of death in these patients (Kerdiles et al 1997). Statin treatment has been shown to be cost effective compared with other medical interventions, and cost effectiveness is related to the efficacy of the drug and the risk of cardiovascular disease (Pickin et al 1999). Consensus health panels, including the Joint British Societies, have established increasingly stringent cholesterol goals, such as a total cholesterol goal of <4.0 mmol/L (JBS2 2005). In view of the increasing amount of data on the benefit of statins, the American Heart Association issued advice in 2004 suggesting that clinicians should consider initiating statin therapy in the hospital for all patients who had suffered stroke of atherosclerotic origin (Das et al 1985; Stroke Council 2004).

Our findings raise even more concern when the plaque histological grading results are considered. We found that patients who had either never had their lipid profiles checked (Group 3) (Table 3) or had hypercholesterolemia (Table 4) seemed to be more likely to have unstable carotid plaques than those in the other two groups. For example, patients with hypercholesterolemia, around 8.3% of all patients, had histological features of plaque rupture, and a quarter of these patients had thin fibrous cap atheroma, which is a high risk plaque for rupture. A study found that an unhealthy life style such as poorly controlled blood pressure, smoking, physical inactivity, and alcoholic consumption correlate well with lipid profile abnormality (Mirjanic-Azaric et al 2006). We found that patients in Group 3 had higher systolic and diastolic blood pressure than patients in the other two groups. Similarly the percentage of patients currently smoking was higher in Group 3 than in other groups. Perhaps those patients with hypercholesterolemia and those in Group 3 have unhealthy lifestyles, which cause active plaque rather than other factors. In other words, poor cholesterol management seemed to reflect poor management of other vascular risk factors. Active plaques in one vascular bed appear to be associated with active plaques in other remote vascular beds. Rothwell et al (2000) studied the angiographic data from the European Carotid Surgery Trial. They found that carotid plaque surface irregularities, believed to arise from plaque rupture and ulceration, predicted an increased risk of arterial disease in other vascular beds including coronary events. Therefore patients who are unaware of any previous cholesterol test have a higher risk of coronary events than those in other groups.

Limitations

There are some limitations to this study. First, only the total cholesterol level was used to demonstrate hyperlipidemia, although high serum low-density lipoprotein (LDL) cholesterol levels may be a better measure of lipid abnormality. When we designed this study however, serum cholesterol was far more widely recognised by patients than serum LDL. Secondly, total cholesterol <5 mmol/L was the recommended level for hypercholesterolemia (JBS1 1998) used during the study period, which is a less stringent cholesterol goal than current criteria (total cholesterol <4 mmol/L) (JBS2 2005). One might think that patients are probably much better treated nowadays. However, in 2007, a study reported that most UK patients (approximately 73%) would not have achieved the goals recently established by the Joint British Societies (Rajagopalan et al 2007). In this study, other atherosclerotic risk factors such as smoking and hypertension were not considered in detail, although they are part of atherosclerotic

risk factor management. Lastly, our sample size might be too small for multivariate analysis.

Conclusions

This study suggests that treatment of hypercholesterolemia in patients for whom CEA is indicated is inadequate in clinical practice, despite much evidence of the benefits of lowering lipid levels. A great deal more effort should be directed at managing blood cholesterol in patients with carotid artery stenosis. These findings support the need for improved education of clinicians and patients in the management of cholesterol levels in patients with vascular disease.

Disclosure

No author has a conflict of interest to disclose.

References

Amarenco P, Bogousslavsky J, Callahan A III, et al. 2006. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*, 355:549–59.

Aspry KE, Holcroft JW, Amsterdam EA. 1995. Physician recognition of hypercholesterolemia in patients undergoing peripheral and carotid artery revascularization. *Am J Prev Med*, 11:336–41.

Barringer TA III. 1997. WOSCOPS. West of Scotland Coronary Prevention Group. *Lancet*, 349:432–3.

Burns P, Lima E, Bradbury AW. 2002. Second best medical therapy. *Eur J Vasc Endovasc Surg*, 24:400–4.

Castelli WP. 1984. Epidemiology of coronary heart disease: the Framingham study. *Am J Med*, 76:4–12.

Cohen MV, Byrne MJ, Levine B, et al. 1991. Low rate of treatment of hypercholesterolemia by cardiologists in patients with suspected and proven coronary artery disease. *Circulation*, 83:1294–304.

Das MB, Hertzer NR, Ratliff NB, et al. 1985. Recurrent carotid stenosis. A five-year series of 65 reoperations. *Ann Surg*, 202:28–35.

Ford I, Murray H, Packard CJ, et al. 2007. Long-term follow-up of the West of Scotland Coronary Prevention Study. *N Engl J Med*, 357:1477–86.

Frolkis JP, Zyzanski SJ, Schwartz JM. 1998. Physician noncompliance with the 1993 National Cholesterol Education Program (NCEP-ATPII) guidelines. *Circulation*, 98:851–5.

Grundy SM, Cleeman JI, Merz CN, et al. 2004. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *J Am Coll Cardiol*, 44:720–32.

[HPS] Heart Protection Study. 2002. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*, 360:7–22.

JBS1. 1998. Joint British recommendations on prevention of coronary heart disease in clinical practice. British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, endorsed by the British Diabetic Association. *Heart*, 80:S1–29.

JBS2. 2005. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart*, 91:1–52.

Kannel WB, Castelli WP, Gordon T, et al. 1971. Serum cholesterol, lipoproteins, and the risk of coronary heart disease. The Framingham study. *Ann Intern Med*, 74:1–12.

Kedward J, Dakin L. 2003. A qualitative study of barriers to the use of statins and the implementation of coronary heart disease prevention in primary care. *Br J Gen Pract*, 53:684–9.

Kerdiles Y, Lucas A, Podeur L, et al. 1997. Results of carotid surgery in elderly patients. *J Cardiovasc Surg* (*Torino*), 38:327–34.

Mirjanic-Azaric B, Deric M, Vrhovac M, et al. 2006. The correlation between lifestyle and lipid profile. *Med Pregl*, 59:57–62.

Musser DJ, Nicholas GG, Reed JF III. 1994. Death and adverse cardiac events after carotid endarterectomy. *J Vasc Surg*, 19:615–22.

NCEP. 2001. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*, 285:2486–97.

Pickin DM, McCabe CJ, Ramsay LE, et al. 1999. Cost effectiveness of HMG-CoA reductase inhibitor (statin) treatment related to the risk of coronary heart disease and cost of drug treatment. *Heart*, 82:325–32.

Rajagopalan S, Alemao E, Finch L, et al. 2007. Impact of new Joint British Societies' (JBS 2) guidelines on prevention of cardiovascular disease: evaluation of serum total cholesterol goal achievement in UK clinical practice. *Curr Med Res Opin*, 23:2027–34.

Rapp JH, Qvarfordt P, Krupski WC, et al. 1987. Hypercholesterolemia and early restenosis after carotid endarterectomy. *Surgery*, 101:277–82.

Rothwell PM, Villagra R, Gibson R, et al. 2000. Evidence of a chronic systemic cause of instability of atherosclerotic plaques. *Lancet*, 355:19–24.

Sacks FM, Pfeffer MA, Moye LA, et al. 1996. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med*, 335:1001–9.

Shepherd J, Cobbe SM, Ford I, et al. 1995. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med*, 333:1301–7.

Stary HC, Chandler AB, Dinsmore RE, et al. 1995. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Arterioscler Thromb Vasc Biol*, 15:1512–31.

Stroke Council. 2004. Statins after ischemic stroke and transient ischemic attack: an advisory statement from the Stroke Council, American Heart Association and American Stroke Association. *Stroke*, 35:1023.

Virmani R, Kolodgie FD, Burke AP, et al. 2000. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol*, 20:1262–75.