EDITORIAL

CHOLESTEROL AND CORONARY ARTERY DISEASE - ISSUES IN THE 1990s

B L Chia

SINGAPORE MED J 1991; Vol 32: 291-294

The three major preventable risk factors for coronary artery disease (CAD) are hypercholesterolaemia, hypertension and cigarette smoking. The more risk factors a person has, the higher will be his chances of suffering prematurely from CAD. Therefore, in the prevention of this disease, a multi-factorial approach is essential. However, it is interesting to note that in certain parts of the world such as in Central Africa and Japan where the serum cholesterol is low, coronary heart disease is infrequent, even though cigarette smoking and hypertension are prevalent[1]. Therefore, it appears that before the other risk factors can achieve their full atherogenic potential, a minimal serum cholesterol level of approximately 160 mg/dL (4.1 mmol/L) or higher is necessary.

CHOLESTEROL (TOTAL, LDL AND HDL) AND TRIGLYCERIDE

The blood total cholesterol consists essentially of 3 major fractions - low density lipoprotein (LDL), very low density lipoprotein (VLDL) and high density lipoprotein (HDL) cholesterol. The LDL cholesterol (which is popularly known as the "bad cholesterol") has for a long time been well known to be highly atherogenic. On the other hand, the importance of HDL cholesterol (popularly known as the "good cholesterol") as a protective factor against atherosclerosis has been recognised only fairly recently. Today, many experts in this field strongly believe that both LDL and HDL cholesterol are equally important major risk factors for CAD, a view which is also held by the author. Since the likelihood of developing atherosclerosis increases with a rise in LDL cholesterol and a fall in HDL cholesterol and since LDL cholesterol generally accounts for about 70% of the total cholesterol, it is only logical to deduce that the ratio of either total cholesterol/HDL or LDL cholesterol/HDL will be an even better predictor of coronary risk compared to either total cholesterol, LDL cholesterol or HDL cholesterol alone. In recent years, this deduction has been confirmed to be true by both clinical as well as epidemiological studies. A total cholesterol/HDL ratio of ≤ 3 connotes a low risk, a ratio of around 4.5 an average risk and a ratio of ≥ 8 a high risk of developing CAD[2].

The level of triglyceride (TG) is frequently inversely related to the HDL cholesterol level. Therefore a high TG level will in general predispose to CAD simply because of the frequently associated low HDL cholesterol level. However, the issue of whether hypertriglyceridaemia per se is atherogenic or not has not been completely resolved. Despite this uncertainty, many experts today believe that hypertriglyceridaemia, which is frequently a result of an elevated VLDL level, is indeed a marker for an increased risk for CAD, especially in diabetic patients and female subjects, although this risk may not be as great as that for an elevated LDL or a low HDL cholesterol.

Department of Medicine
National University Hospital
Lower Kent Ridge
Singapore 0511

B L Chia, MBBS, FRACP, FACC
Professor

EVALUATION OF LIPID ABNORMALITIES

In the evaluation of coronary risk in an individual person, the determination of serum total cholesterol, HDL cholesterol and TG levels from a fasting blood specimen is recommended. From these 3 values (all of which must be in mg/dL), the LDL cholesterol level (in mg/dL) can be obtained using a very simple mathematical formula: LDL = total cholesterol - (HDL cholesterol + TG/5). If the serum TG is higher than 400 mg/dL, this formula is invalid and the LDL cholesterol level must be measured directly if it is needed[3].

It is very important to be aware that the current methods of estimating serum total cholesterol are far from ideal and that there is a 2 - 5% co-efficient variation in the analysis even in good laboratories. It is therefore recommended that if the initial estimation of serum total cholesterol is elevated, it should be repeated before any decision is made regarding whether the person has hypercholesterolaemia or not. If the first and second estimation vary by $\leq$ 30 mg/dL (0.8 mmol/L), the total cholesterol level should be regarded as the mean of these 2 levels. If the variation exceeds 30 mg/dL, a third estimation should be done and all 3 estimations should then be averaged. The present methods for determining HDL cholesterol are even more imprecise and hence the variability is even greater than that for total cholesterol estimation. Therefore, small differences in the values derived from consecutive estimations of the HDL cholesterol level should not be regarded as reflecting genuinely significant changes in this lipid fraction. Since the LDL cholesterol level is calculated from both the total cholesterol, HDL cholesterol and TG levels, it is not surprising that there is also considerable variability in the estimation. Similar to the total cholesterol estimation, the LDL cholesterol estimation should also be repeated if the initial value is elevated. If the first and second estimation vary by $\leq$ 30 mg/dL (0.8 mmol/L), the LDL cholesterol level should be regarded as the average of these 2 values.

It has been stated that a total cholesterol level of $\geq$ 240 mg/dL (6.2 mmol/L) represents "high blood cholesterol", a level between 200-239 mg/dL (5.2 - 6.2 mmol/L) a "borderline-high blood cholesterol" and a level < 200 mg/dL (5.2 mmol/L) a "desirable blood cholesterol", implying a high, a moderately high, and a low risk of developing CAD[3]. However, the actual significance of a total blood cholesterol level alone in any individual may be quite misleading. For example, in subjects where the total cholesterol levels are around 240 mg/dL (a very common clinical situation), the LDL cholesterol levels may vary considerably and the total cholesterol/HDL or LDL cholesterol/HDL ratios may be high (as in subject B), medium (as in subject A) or low (as in subject C), depending entirely on the relative levels of the total, LDL and HDL cholesterol levels (Table I). This again underscores the importance of determining both the LDL and HDL cholesterol levels, rather than depending entirely on the total cholesterol

level alone for the evaluation of coronary risk. Even in subjects with a total cholesterol of 200 mg/dL (5.2 mmol/L) or lower, the risk for CAD may be considerable if the HDL cholesterol is low. This was highlighted in the renowned Framingham Study in the United States of America where 15% of the patients with acute myocardial infarction had a total cholesterol of only 150 - 200 mg/dL (3.9 - 5.2 mmol/L) but also a low HDL cholesterol[4]. In a study of 70 subjects with a total cholesterol of ≤ 200 mg/dL (5.2 mmol/L) which was carried out by the author, it was found that the total cholesterol/HDL ratios varied from as low as 1.8 (an ideal situation) to as high as 8.5 (a highly undesirable situation) (Figure).

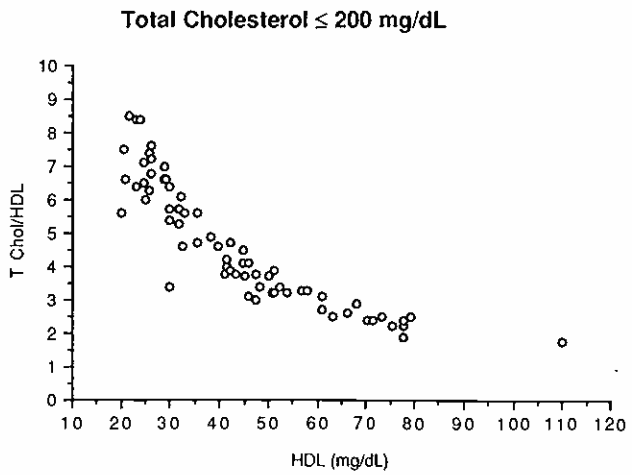
Table I

This table shows that in subjects whose total cholesterol is around 240 mg/dL (6.2 mmol/L), the risk for coronary heart disease may be low (subject C), medium (subject A) or high (subject B) depending entirely on the relative levels of the total, LDL and HDL cholesterol levels (see text). Abbreviations: Total chol = total cholesterol, TG = triglyceride, HDL = HDL cholesterol, LDL = LDL cholesterol, T Chol/HDL = total cholesterol/HDL cholesterol ratio, LDL/HDL = LDL cholesterol/HDL cholesterol ratio.

	A	B	C
Total Chol	240 mg/dL (6.2 mmol/L)	240 mg/dL (6.2 mmol/L)	240 mg/dL (6.2 mmol/L)
TG	150 mg/dL (1.7 mmol/L)	200 mg/dL (2.3 mmol/L)	150 mg/dL (1.7 mmol/L)
HDL	55 mg/dL (1.4 mmol/L)	25 mg/dL (0.6 mmol/L)	80 mg/dL (2.1 mmol/L)
LDL	155 mg/dL (4.0 mmol/L)	175 mg/dL (4.5 mmol/L)	130 mg/dL (3.4 mmol/L)
T Chol/HDL	4.4	9.6	3
LDL/HDL	2.8	7.0	1.6

Figure

This figure shows the relationship between the total cholesterol/HDL (TChol/HDL) ratios and the levels of the HDL cholesterol in 70 subjects whose serum total cholesterol was ≤ 200 mg/dL (5.2 mmol/L).



APOLIPOPROTEINS, LIPOPROTEIN (a) AND CORONARY ARTERY DISEASE

Recently, several studies involving coronary angiography have demonstrated that certain apolipoproteins eg Apo A1 and Apo B are as good or even better predictors of coronary atherosclerotic disease compared to LDL and HDL cholesterol. Apo A1 , like HDL cholesterol, has been shown to be protective and Apo B, like LDL cholesterol, to be atherogenic. In recent years, lipoprotein(a) or Lp(a) has also been shown to be highly atherogenic. However, at present, apolipoprotein estimation on a routine basis is not recommended but should be considered in patients with CAD or in those who have multiple coronary risk factors, especially if their LDL cholesterol, HDL cholesterol or TG levels are normal.

INDIANS AND CORONARY ARTERY DISEASE

It has been widely known for many decades that the Indians in Singapore have an approximately threefold increased risk of developing CAD compared to the Chinese and Malays. It has always been stated, but never proven, that this is due to their diet which is believed to be high in cholesterol and saturated fat content, thus resulting in a high serum LDL cholesterol level. This hypothesis is most likely incorrect because in a recent study by Hughes and co-workers, the serum total cholesterol, LDL cholesterol and TG levels amongst the Indians, Chinese and Malays in Singapore were found to be almost identical[5]. A very interesting and important finding in this study was that although the HDL cholesterol levels in the Chinese and Malay males were low (approximately 34 mg/dL) (0.9 mmol/L), the levels in the Indian males were even lower (around 27 mg/dL) (0.7 mmol/L). Despite the lower HDL cholesterol level and a higher prevalence of diabetes mellitus in Indian males compared to Chinese and Malay males, the magnitude of these 2 differences is insufficient to completely account for the very marked increase in CAD seen in Indians. Therefore, why Indians in Singapore and also elsewhere are so prone to CAD still remains a mystery after more than 30 years and the answer (if any) must await further research.

MANAGEMENT OF DYSLIPIDAEMIA - GENERAL RECOMMENDATIONS

Most of the major studies regarding the benefits of treatment of hyperlipidaemia have involved LDL cholesterol. It is therefore not surprising that guidelines for treating lipid abnormalities which have been issued so far - eg National Cholesterol Education Programme (NCEP) - have focused attention mainly on LDL cholesterol[3]. In the NCEP guidelines for adults, the recommended goal LDL cholesterol level vary according to whether a person has either: (1) CAD or (2) any 2 of the following risk factors: (a) male sex (b) family history of premature coronary heart disease (c) cigarette smoking (d) hypertension (e) HDL cholesterol < 35 mg/dL (0.9 mmol/L) (f) diabetes mellitus (g) history of definite cerebrovascular or occlusive peripheral vascular disease and (h) severe obesity (≥ 30% overweight). The goal LDL cholesterol level is < 130 mg/dL (3.4 mmol/L) if the subject has either (1) or (2) and < 160 mg/dL (4.1 mmol/L) if he has neither. It is important to remember that these recommendations are minimal goals and if lower levels can be achieved, the risk may be further reduced.

The first step in the strategy for lowering LDL cholesterol is always dietary measures which must be vigorously pursued. However, the compliance to dietary treatment is generally poor and optimal results are frequently not obtained. The NCEP has recommended that after dieting has been implemented, drug therapy should be considered in 2 situations: (1) in individuals whose LDL cholesterol levels remain ≥ 160 mg/dL (4.1 mmol/L) and who have either CAD or 2 of the risk factors listed above or (2) in individuals whose LDL cholesterol levels are above ≥ 190 mg/dL (4.9 mmol/L) and who have neither CAD nor any 2 risk factors. Many critics agree that these guidelines are by and large applicable to middle-aged men, but have questioned whether it is appropriate to generalise these recommendations to include also elderly subjects and women (especially those who do not have CAD), since there have so far been no trials to study the value of drug therapy in these 2 groups of subjects.

Although a low HDL cholesterol is an important coronary risk factor, there is at present considerable debate and uncertainty whether pharmacological therapy is indicated in this situation. This is so because there have been no trials so far accessing the value of elevating an isolated low HDL cholesterol level. Although it has been widely publicized that the Helsinki Heart Study demonstrated that elevation of HDL cholesterol can significantly reduce the incidence of coronary heart disease, this trial was actually designed primarily to test the hypothesis whether lowering of non-HDL cholesterol (ie LDL and VLDL cholesterol) is beneficial and not to study the value of increasing HDL cholesterol per se[6]. In subjects with low HDL cholesterol, non-pharmacological measures such as exercise, weight reduction, and most importantly, stopping cigarette smoking should always be pursued. At present, there is a greater tendency amongst physicians to begin treatment with drugs such as fibrates or nicotinic acid if the low HDL cholesterol is associated with either an elevated TG or LDL cholesterol or if the patient already has CAD. Similarly, criteria for starting drug therapy in patients with isolated hypertriglyceridaemia have also not been defined. Indeed, many experts do not advocate drug treatment except when the hypertriglyceridaemia is a manifestation of genotypic familial combined hyperlipidaema or when the TG is between 500 - 1000 mg/dL (5.6 - 11.3 mmol/L) despite dietary measures.

PHARMACOLOGICAL THERAPY

One of the basic principles regarding drug therapy of dyslipidaemia is that it should be started only in situations where the potential benefits outweigh the risks. This is because all the current anti-dyslipidaemic agents have some side effects and many of them are also quite expensive. In general, the more severe the dyslipidaemia, the greater will be the benefits of drug therapy. The 4 most important groups of drugs that are widely available today are: (1) bile-acid sequestrating resins eg cholestyramine (questran) (2) fibrates - eg gemfibrozil (lopid), bezafibrate (bezalip) and fenofibrate (lipanthyl) (3) HMG CoA reductase inhibitors - eg lovastatin (mevacor) and simvastatin (zocor) and (4) nicotinic acid (niacin).

Table II shows the percentage reduction of LDL cholesterol and TG and the percentage elevation of HDL cholesterol which can be achieved with these drugs. It is clear that the HMG CoA reductase inhibitors, the bile-acid sequestrants and nicotinic acid are the most powerful agents for lowering LDL cholesterol. The fibrates and nicotinic acid reduce TG markedly and also elevate HDL cholesterol modestly. The main disadvantages of cholestyramine are its unpleasant taste and its high incidence of gastrointestinal side effects, both of which result in a low compliance to this drug. However, cholestyramine is a very well tested pharmacological agent and has a high safety profile. The 2 main advantages of the HMG CoA reductase inhibitors are their very marked lowering of the LDL cholesterol and their low incidence of side effects. Their main disadvantages, apart from the high cost, are: (1) it is necessary to monitor closely patients who are taking this group of drugs for significant liver dysfunction and elevation of muscle enzymes, both of which fortunately occur infrequently and (2) the experience with the HMG CoA reductase inhibitors is not as long as that for the other drugs. At present, only simvastatin (zocor) is available in Singapore. The fibrates have a very small incidence of side effects and are generally well tolerated. Although they lower TG very effectively, reduction of LDL cholesterol is generally much less impressive, with bezafibrate and fenofibrate reducing LDL cholesterol more than gemfibrozil. Nicotinic acid is an excellent drug for lowering total cholesterol, LDL cholesterol, TG and for elevating HDL cholesterol. It is also one of the cheapest drugs that are currently used for the treatment of dyslipidaemias. In this era of constant awareness of cost-effectiveness, this is obviously an important advantage. However, because of its strong side effects, nicotinic acid is not widely used clinically. Acipimox (olbetam) is a derivative of nicotinic acid and has been reported to be as effective as the parent drug with fewer side effects. However, experience with this drug is limited and its exact place in the therapeutic armamentarium is at present unclear. Although fish oil is very much in the limelight, its actual role is currently very limited. Its main indication is in cases of severe hypertriglyceridaemia which have not responded adequately to the other drugs.

In type IIA hyperlipidaemia, where only the total cholestrol and LDL cholesterol are elevated, either a bile-acid sequestrating resin, a HMG CoA reductase inhibitor or nicotinic acid should be given. Combination of the first 2 drugs is very effective, especially in patients with very high LDL cholesterol levels. In type II B hyperlipidaemia where there is elevation of the total, LDL and VLDL cholesterol as well as TG, nicotinic acid, fibrates or HMG CoA reductase inhibitors are recommended. In the author's experience, gemfibrozil (lopid) will nearly always lower the TG markedly. However, reduction of LDL cholesterol is far less predictable and sometimes it may even become elevated. In many patients, a bile-acid sequestrating resin (eg cholestyramine) will have to be combined with gemfibrozil before the LDL cholesterol can be adequately lowered. The combination of these 2 drugs is an excellent form of therapy for many patients with type IIB hyperlipidaemia. In type IV hyperlipidaemia where the TG is elevated and the HDL cholesterol is frequently low, both gemfibrozil and nicotinic acid will markedly lower the high TG. They will often also modestly elevate the HDL cholesterol.

Table II

Table showing the percentage reduction or elevation of the various lipid fractions with the different drugs. *Note that LDL cholesterol reduction by gemfibrozil (lopid) is around 10% and by both bezafibrate (bezalip) and fenofibrate (lipanthyl) is around 25% (see text). Abbreviations: LDL = LDL cholesterol, HDL = HDL cholesterol, TG = triglyceride, ↓ = reduction, ↑ = elevation, - = no change.

Drug	LDL	HDL	TG
Resins	↓ 15-35%	-/↑4%	-/↑
HMG CoA Reductase Inhibitors	↓ 25-40%	↑ 5-10%	↓ 15-20%
Fibrates	↓ 10-25%*	↑ 10-15%	↓ 50%
Nicotinic Acid	↓ 15-35%	↑ 10-25%	↓ 50%

PREVENTION, RETARDING PROGRESSION AND REGRESSION OF CORONARY ARTERY DISEASE

The recent Lipid Research Clinic trial in the United States of America demonstrated that treatment with cholestyramine will decrease the incidence of coronary heart disease in asymptomatic men whose serum total cholesterol remains ≥ 265 mg/dL despite diet therapy. It was also shown in this study that a 1% reduction of total cholesterol will result in a 2% reduction of heart attacks but there was no reduction in total mortality[7]. However, it is important to remember that this trial was done in middle-aged, healthy American men. Whether the same potential benefit can be obtained in women or elderly subjects is at present unknown. The Helsinki Heart Study showed that in healthy middle aged men with elevated non-HDL cholesterol (ie LDL and VLDL cholesterol), gemfibrozil significantly reduces the risk of subsequent

coronary heart disease[6]. Sophisticated statistical analyses revealed that the beneficial effect was largely due to both the lowering of the LDL cholesterol as well as the elevation of the HDL cholesterol. In post-myocardial infarction patients, the Coronary Drug Project study in the United States of America showed that nicotinic acid resulted in a reduction in the incidence of subsequent non-fatal infarcts and a decrease in total mortality[8]. In patients who have established CAD, sequential coronary angiographic studies have shown that aggressive treatment using combination drug therapy resulting in marked lowering of the total cholesterol, LDL cholesterol, and TG, together with elevation of the HDL cholesterol, can retard the progression of coronary atherosclerosis as well as cause regression of established coronary atherosclerotic lesions[9].

CONCLUSION

The interest, anxiety and the controversies regarding the relationship between lipids and CAD and its management amongst family physicians, epidemiologists, cardiologists, the general public, administrators and experts in this field have never been greater as we enter into the 1990s. Despite all these uncertainties, the author personally believes that the major importance of a significantly elevated LDL cholesterol and a low HDL cholesterol should be fully recognized and should not be ignored in the current light of our knowledge. Careful clinical evaluation and skilful interpretation regarding the significance of the levels of the various lipid fractions which have been obtained from the laboratory tests are both crucial to successful management. All patients with significant lipid problems requiring treatment should be advised to pursue dietary measures vigorously in the initial management. In certain subsets of patients where the LDL cholesterol level remains high or especially if the hypercholesterolaemia is associated with CAD, there is little doubt that the potential benefits of drug therapy far outweigh the risk and should therefore be instituted without any hesitation or delay.

References

1. Roberts WC. Extreme hypercholesterolaemia - malignant atherosclerosis. Am J Cardiol 1984; 54: 242.
2. Castelli WP. Low HDL cholesterol as a predictor of CHD risk. Internal Medicine for the specialist. September 1989.
3. The Expert Panel. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Arch Intern Med 1988; 148: 36-69.
4. Castelli WP. Lipoproteins as risk factors in coronary artery disease (symposium report). Medical Progress. April 1990.
5. Hughes K, Yeo PPB, Lun KC, et al. Ischaemic heart disease and its risk factors in Singapore in comparison with other countries. Ann Acad Med Singapore 1989; 18: 245.
6. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. Engl J Med 1987; 317: 123-45.
7. The Lipid Research Clinics Program: The Lipid Research Clinics Coronary Primary Prevention Trial Results, II: relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA 1984; 251: 365-74.
8. Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in Coronary Drug Project patients - Long term benefit with niacin. J Am Coll Cardiol 1986; 8: 1245-55.
9. Blankenhorn DH, Nessim SA, Johnson RL, Sanmarco ME, Azen SP, Cashin-Hemphil L. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. JAMA 1987; 257: 3233-40.