Lipids

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Introduction

This background discussion summarises guidelines from a number of sources world wide.[1-7] These guidelines make use of similar, current and best evidence in published literature and are thus similar in their conclusions and recommendations. Where possible local information (Northern Territory (NT) data) are used to address relevance of the topic to remote NT health practitioners.

Population and high risk strategies: concepts

Population strategies seek to prevent or delay the onset of coronary heart disease (CHD) in whole populations. The high-risk approach concentrates its efforts on the smaller number of individuals with cholesterol above a certain threshold defining hypercholesterolaemia.

This background document concentrates on the targeting of high-risk individuals in a clinical context. But it must be noted that effective CHD prevention must involve population (public health and health promotion strategies) as well as high risk approaches, and that these are not mutually exclusive.

Need for primary prevention of CHD through lipid control

Diseases of the circulatory system, such as ischaemic heart disease and cerebrovascular disease, are a major cause of mortality among Indigenous males and females, accounting for more than one in four deaths identified as Indigenous. There are almost three times as many cardiovascular deaths as expected among Indigenous males and females, based on the all-Australian rates. The rates of death from circulatory diseases are higher for Indigenous males and females than for their all-Australian counterparts in every age group from 15 to 74 years, and the steep rise in death rates begins many years earlier (10–20 years earlier in the NT[8]) among Indigenous people than among all-Australian males and females. Ischaemic heart disease is responsible for the largest number of deaths from circulatory disease among Indigenous males and females.[9] In the NT, from 1979 to 1995, ischaemic heart disease was the leading cause of death of Indigenous people at 11.7% of all deaths.

A number of observational data exist that relate the extent of cardiovascular risk factors in Aboriginal populations. It has been observed that in more traditional Aboriginal groups total cholesterol (TC) levels were not generally elevated even when compared to general Australian populations.[10,11] However, high-density lipoprotein-cholesterol (HDL-C) levels were significantly lower than Australian population, and thus LDL-C/HDL-C (low density lipoprotein-cholesterol) ratios tended to be high.

In one study in coastal Arnhem Land, where 78% of the 25–64 year old Aboriginal population participated, 74% of subjects had LDL-C/HDL-C ratio greater than 4.5 (abnormally high). In these studies high triglyceride (TG) were widespread and were much higher in men than women (occurring in 56% of males and 35% of females in Arhnem Land). Similar observations were noted in Central Australian Aborigines and represented a high-risk profile for coronary heart disease (CHD).[12] Total cholesterol tended to increase with age.

In another study in Central Australia TC were elevated in 68% of men and 46% of women over 35 years old. A significant proportion of men and women under 35 years old had elevated TC (48% and 41% respectively) as well. There was a similar problem with TG. The rise in TG and TC with age was reciprocated with a fall in HDL-C.[13] The difference in the two studies in Central Australia relates to the difference in prevalence of other CHD risk factors, like overweight and obesity and diabetes in the two sample groups. O'Dea's group shows that the problem of dyslipidaemia is already present in young adults and that it would be appropriate for intervention programs to target young people.[12]

Lipids in the context of other CHD risk factors

Although lipids are the main focus of this background paper, cholesterol lowering is only one of a number of interventions to reduce CHD risk. There is a recent overview of trials of multiple risk factor lifestyle interventions for preventing CHD that pooled data from 14 randomised comparisons of multifactorial intervention comprising 1 000 000 person years of observation.[14] The systemic review reports on the main outcome of decrease in BP of 2.3/1.1 mmHg where anti-hypertensive drugs were not used, a reduction of smoking prevalence of 4.2% and a net decrease in serum cholesterol of 0.14 mmol/L. These changes were associated with a non-significant fall in CHD mortality of 4% and total mortality of 3%. It was concluded that health promotion interventions resulted in only small changes in risk factors and mortality rates in the general population, although there were beneficial effects in individuals within high-risk groups.[14]

There are a number of explanations for this, including lack of motivation leading to poor compliance. These in turn may be linked to poor socioeconomic status, raising the possibility that until poverty and deprivation are tackled effectively, the benefit of a healthy lifestyle may never be realised by a substantial proportion of the population.

It should be noted that for those who are able to make the necessary changes the benefits might be considerable. Small average reduction in risk factors may have concealed much larger gains for those who were at highest risk initially.[13] Appropriate lifestyle measures should always be attempted before resorting to drug therapy.[1–6] Lifestyle measures may influence the whole family and not just the individual at risk. On the other hand people who do not respond to promotion of lifestyle changes are still likely to benefit from drug therapy if it is needed.

Measures for lifestyle change include:

Stop smoking

The risks of smoking on CHD increase with the amount of tobacco smoked daily and the duration of smoking. All patients should be actively discouraged from smoking. Repeated brief and supportive advice on smoking cessation should be given to patients by the primary care team. Drug (e.g.

nicotine replacement) therapy should be considered routinely in smokers with the motivation to quit because they double the quit rate at one year.[15]

Dietary advice

The main dietary determinant of serum cholesterol is not dietary cholesterol but saturated fat. Further, there are many components of a healthy diet that are not related directly to lipids, but which affect CHD incidence. Diets naturally rich in antioxidants (fruit and vegetables) may be protective against CHD [Editor: An RCT of antioxidant supplementation failed to confirm this suspected cause-and-effect relationship, so it may be a more complex issue of cuisine rather than a specific micronutrient that is important, i.e. antioxidant supplements are not a substitute for a healthy diet.]

A number of studies have documented low rates of fruit and vegetable consumption in Indigenous communities around Australia. Consequently, a higher intake of fruit and vegetables is recommended. Dietary fibre, oily fish and mono-saturated fatty acids may also be protective against CHD. Bush foods, in particular meat, have been known to have low fat content and organ meats contain long chain highly polysaturated fatty acids.[16]

Low fat diets in studies with high compliance saw a reduction in serum cholesterol of 10–15%. By contrast, community-based studies have shown much smaller average changes. For example, 3% reduction in an American Heart Association (AHA) step 1 diet and 6% for an AHA step 2 diet (AHA step 1 and step 2 diets advise less than 30% of total calories as fat).[4]

In Aboriginal populations, community-based nutrition intervention programs have been implemented in some communities and have shown some improvement in nutritionally related health outcomes. In one study of a community intervention project a reduction in TC of 12% was observed together with improvements in blood pressure and red cell folate.[17] Furthermore, these studies have shown that appropriate facilitating, planning, implementation and ownership of interventions by community members and organisations can lead to sustained nutritional improvements.[18]

A meta-analysis of epidemiological (ecological) studies showed that there is linear, independent relationship between homocysteine concentration and cardiovascular risk. Homocysteine levels can be easily and effectively reduced by supplementation with folic acid alone or in combination with vitamins B6 and B12.[19] Clinical trials are underway to evaluate the impact of folate supplementation on reducing clinical cardiovascular events. Until these studies are reported it is not possible to make a recommendation on vitamin supplementation with folic acid as a preventive measure for CHD.

It is well known that dietary salt (sodium) intake has an adverse effect on blood pressure and potential effects on CHD and strokes. Dietary salt restriction should also be considered. A meta-analysis of primary prevention dietary intervention has estimated that a reduction in sodium intake of 30 mmol/d is achievable among normotensive and mildly hypertensive individuals.[20] Dietary sodium intake should be reduced towards recommended levels of 100 mmol, or 6 g of salt per day.

Obesity and overweight

Obesity (BMI >30 kg/m^2) and being overweight (BMI >25) has an adverse influence on a number of cardiovascular risk factors including BP, plasma cholesterol, triglycerides, glucose tolerance and is a risk factor for thrombogenesis in its own right.[21] Risk increases substantially in people

with a BMI >30, particularly those people with excess intra-abdominal fat. Waist circumference offers a simple indicator of risk. However, there are no primary prevention trials that show that weight reduction impacts directly on CHD, although observational data suggest an ideal BMI between 18.5–25.[21]

Realistic targets of 5–10 kg weight loss should be set for overweight and obese individuals. A successful strategy for weight loss will include advice not only on diet and exercise but also on behavioural change, support systems and maintenance of reduced weight.[22] [Editor: This is discussed further in the 'Overweight and obesity in adults' chapter.]

Physical activity

Prospective studies support the view that a sedentary lifestyle is associated with an increased risk of CHD. Physical activity leads to a reduction in TC and LDL-C and a concomitant increase in HDL-C.[23] Moderate physical exercise decreases mortality. For those who are inactive or not regularly active, aim to accumulate 30 minutes of moderate intensive physical activity on most days. For those who are already active, vigorous aerobic exercise of 20–30 minutes three times per week is recommended.[24]

Socioeconomic and psychosocial status

There is increasing evidence of a relationship between low socioeconomic status (SES) and poor health, both for general health and across a range of conditions including type 2 diabetes, dyslipidaemia and CHD.[25] Many Aboriginal people live in poor socioeconomic circumstances, with limited incomes and poor household living conditions compounded by low levels of education, high rates of unemployment and the effects of displacement from traditional lands and cultural environments. These problems exacerbate health conditions by acting as a barrier to self-management and control and increasing the risk of complications. SES impacts upon risk factors for CHD, including physical inactivity, overweight and smoking.[25]

There is growing evidence that low SES may be a risk factor in its own right, as well as impacting on other factors and health service access. Low mastery (the extent to which people feel control of the forces affecting their lives) and poor mental health (depression) are related to the development and progression of CHD.[26] Furthermore, there is association between perceived control (mastery) and positive mental health (lack of depression) to healthy HDL-C levels. Positive effects on mental health enhance the immune function and attenuate stress-related changes in cholesterol.[27]

Links between psychosocial status and cholesterol may exist via neuroendocrine pathways. Research is looking more and more into this area. The practical implication of this is that energy should be focused on ways to improve health service interaction with people in remote Aboriginal communities.[26] However, the uncritical application to Aboriginal people of therapies suitable for non-Aboriginal persons may not be effective.

For example, on-going monitoring, education and dealing with variable 'compliance' is complicated by cultural differences in basic value systems, communication patterns and social structure, all of which are potential barriers to deriving benefit from Western medical knowledge. The value placed on respect and autonomy in Aboriginal culture may lead Aboriginal people to regard Western style of intervention as interference, interruption of lifestyle or invasion of privacy.[26]

Educational interactions that are culturally appropriate and orientated towards communication and empowerment may be necessary. Elucidating Aboriginal beliefs about the causes of diseases and relating them to Western biomedical concepts for management of diseases could enhance mastery.[26] Further inroads into the links between mental health and physical illness is required. [Editor: Some risk factors for cardiovascular disease are discussed here, but readers should realise that this is not exhaustive.]

How long to trial lifestyle measures before considering drug therapy for lipids?

There are no studies to indicate how long a trial period of lifestyle measures should last before considering lipid-lowering drug therapy. In a meta-analysis of dietary intervention trials, the total cholesterol reduction attributable to dietary advice was 6.6% at six weeks, 8.5% at three months and 6.8% at six months.[28] Therefore, it is preferable to pursue lifestyle changes for at least three to six months in individuals whose absolute risk for CHD is closer to 3% per year when their chance of experiencing a cardiovascular event is relatively low.[4] Patients at very high risk may justify drug therapy at an earlier stage. Lifestyle measures should continue beyond three months irrespective of the use of pharmacological treatment.

The role of lipid-lowering drugs for high-risk patients

Statins

Statins (HMG CoA reductase inhibitors) influence the rate-limiting enzyme in cholesterol synthesis. They rapidly lower serum total cholesterol, especially LDL-C. They also have a lesser effect on TG and very low-density-lipo-protein-cholesterol (VLDL-C). They also cause a small rise in HDL-C.[29]

Pravastatin, simvastatin and lovastatin have been assessed in clinical trials (pravastatin in primary and secondary prevention (WOSCOPS[30], CARE[31], and LIPID[32]); lovastatin in primary prevention (AFCAPS/TexCAPS[33]) and simvastatin in secondary prevention (4S[34])). The relative reductions observed with these three statins were similar, suggesting a class effect in CHD event reductions and no increase in non-cardiovascular deaths. Other benefits include a reduction in coronary revascularization procedures and strokes and may include reduction in the incidence of anginal symptoms, congestive heart failure, disability and improved quality of life.

Hepatoxity is the most common serious side effect occurring in 1% of patients. Liver function tests should be monitored before and once during therapy but not again if normal. Rhabdomyolysis is the most serious adverse effect occurring in <0.1% of patients.

Fibrates

Fibrates lower serum TG and increase HDL-C levels but have less effect on LDL-C and TC levels when compared to statins. There have been two primary prevention clinical trials involving fibrates: the WHO Clofibrate trial and the Helsinki Heart study of gemfibrozil.[35] Both studies showed a reduction in CHD events. The Clofibrate trial saw an increase in non-coronary mortality. There was a non-significant increase in non-coronary mortality in the Helsinki study, which meant all cause mortality was not reduced. Fibrates

cannot be recommended as first line agents for the primary prevention of IHD.[4]

There are two secondary prevention studies.[7] One clinical trial using gemfibrozil for about five years saw a significant reduction in non-fatal MI and coronary deaths compared to placebo. The second clinical trial using bezafibrate did not see any significant differences between placebo and treatment group over the six-year trial period.

Fibrates are indicated for mixed hyperlipidemia, hypertriglyceridemia or when statins are poorly tolerated or ineffective. It is suggested that in high risk subjects when both cholesterol and TG are >5.0 mmol/L fibrates can be used.

Fibrates are well tolerated although myopathy is a recognised side effect.

Resins

Resins (cholestyramine and colestipol) are anion-exchange compounds that bind bile acids preventing their reabsorption. Two primary prevention trials involved colestipol (Upjohn study) and cholestyramine (Lipid Research Clinics Coronary Primary Prevention Study). Both studies showed a reduction in CHD events.[4] They also showed non-significant increases in non-coronary mortality. Resins are not recommended as first-line agents for primary prevention of CHD.

Other lipid lowering agents

Nicotinic acid group, fish oil (omega 3 marine TG) and soluble fibre (ispaghula husk) have not been assessed in primary prevention outcome studies. Their use should be discussed with a specialist.

Combination therapy

There are no primary prevention studies using combinations of lipid-lowering agents (statins plus fibrate or statin plus resin for the treatment of refractory hyperlipidemia, or for enhanced efficacy compared monotherapy). There is a small risk of myopathy that exists with statins and fibrates that appears to increase when they are used together and in the presence of renal impairment.[4] A specialist should assess patients who require combination therapy.

Intervention threshold: When should patients be offered lipid-lowering drug therapy as primary prevention?

Who to assess

Whole population screening for hyperlipidemia is not recommended.[4,5] Lifestyle programs that are directed at whole populations together with a targeted approach for high-risk people should be adopted. Assessment may be undertaken systematically by targeting specific groups likely to be at increased risk of CHD, e.g. diabetics and hypertensives. Patients may be assessed opportunistically during contact with primary health care services.

In mainstream populations there is good evidence to screen for primary prevention of dyslipidaemia in people more than 35 years old.[1–6] Below 35 years the risk of CHD is too low to justify widespread screening.[1–6] Further, there are no randomised prospective trials that have assessed long-term lipid-lowering therapy in this age group (20–35 year olds) so no evidence-based recommendation can be made. Even so some reputable groups do recommend starting screening for primary prevention from 20 years old.[5] For patients more than 70 years old there is a lack of evidence of benefit for intervention. The exceptions for this are members of families of patients with inherited dyslipidaemia (familial cholesterolaemia) including children.

Having cited the above argument in mainstream populations one must consider the differences in Aboriginal populations where there are higher rates of dyslipidaemia as well as diabetes and CHD at a significantly younger age of about 10–20 years[8] (see above). It is the author's opinion that it is logical to adopt the lower age group of 20 years old as the age to start routine screening for dyslipidaemia for the primary prevention of CHD in Aboriginal populations of the Northern Territory. This takes into consideration that atherosclerosis begins long before clinical manifestations and that more modest interventions, such as diet and weight loss, can be used early in such individuals.

Patients with a history of CHD, CVD and PVD should be case-managed and this will include a more aggressive approach to lipid monitoring (see below).

In certain circumstances cholesterol levels may not be representative of a patient's usual levels. These situations include acute illness, hospitalisation, weight loss, pregnancy, lactation or MI within the previous 6–12 months. Lipid assessment should be delayed under these circumstances or interpreted with caution.[1–6]

Which test?

The best lipid predictor of coronary risk at present is the ratio of TC to HDL-C.[6] The TC/HDL-C ratio reflects both the adverse effect of non-HDL-C and the protective effect of HDL-C on atherosclerosis, thrombogenesis and blood viscosity.[4]

Serum TG is elevated after a fatty meal and often in diabetes, obesity, alcohol excess and liver disease. Measurement of TG after 12 hours of fasting is recommended to obtain an accurate measurement of baseline levels.[1–6]

Direct measurement of LDL-C is expensive and is only rarely necessary. Such tests, when indicated, should be ordered by specialist consultants. LDL-C can be derived indirectly from Friedewald formula:
LDL-C (mmol/L) = TC – HDL-C – 0.45 x TG [Only valid if TG <4.0 mmol/L]

Exclusion of secondary causes of hyperlipidaemia

Secondary causes of dyslipidaemia should be excluded. Serum TC is usually raised in hypothyroidism and nephrotic syndrome (therapeutic guidelines).[36] Raised TG may be associated with diabetes, alcohol excess and liver disease. Suggested minimum requirement for further tests to exclude secondary causes include:

- Electrolyte, creatinine and urea
- Urinalysis
- Fasting glucose
- Liver function test
- Thyroid stimulating hormone (TSH) if serum cholesterol ≥8.0

Remember drugs (β-blockers, thiazide diuretics, oral corticosteroids, oral contraceptives, phenytoin, cimetidine, cyclosporin, oral retinoids and protease inhibitors for HIV infection) may affect lipid metabolism.

Risk assessment

The perception of the value of lipid-lowering drug therapy has changed. Previously concern was expressed that any benefit for CHD might be offset by an increase in non-cardiovascular mortality. This is not the case for statins. Of greater interest is the identification of patients whose risk of developing CHD justifies lipid-lowering drug therapy for primary prevention.

Intervention trials confirm that those at highest risk of CHD events have most to gain by treatment. The best way to target patients for statin therapy is to calculate the absolute risk, not simply cholesterol level, which is a poorer predictor of risk.[36–38] Given that the placebo event rates for CHD death or non-fatal MI in the CARE and LIPID studies are in the order of 3% pa, it is logical to target a similar coronary event rate in primary prevention with a statin.[4]

Guidelines for risk assessment

A number of tools have been published which can be used for risk stratification e.g. the Sheffield Table[36], the NZ Guidelines[37] and the Joint British Societies Coronary Prediction Chart.[38] All three risk assessment methods use the Framingham risk equation to determine the risk of a major cardiovascular event. The practical utility of these tools has been evaluated. Nurses and doctors interpreted the NZ guidelines and Joint British Chart more accurately and prefer these to the Sheffield table. The cardiovascular risk assessment using tables and charts was acceptable to primary health care professionals.[4]

The main purpose of the above guidelines were to show whether an individual risk of CHD is increase using age, sex, serum TC, and presence of HT, smoking, diabetes and electrocardiographic left ventricular hypertrophy as risk factors. These risk charts, therefore, may underestimate risk (due to their exclusion) of: Australian Indigenous populations; diabetics with nephropathy (proteinuria or microalbuminuria); those with familial hypercholesterolaemia; strong family history of

premature CHD; chronic renal disease (sCr >150 mmol/L); those who have recently stopped smoking or started antihypertensive drug treatment; or those who are at the top of their age range (because risk for each age band (e.g. 55–64) is calculated at the mid point (e.g. 60).[4] Risk will be underestimated as patients approach the next age category).

It can be recommended that a patient should be considered for lipid-lowering drug therapy for primary prevention following a trial of lifestyle measures and other appropriate interventions for at least three months when the TC is ≥5.0 mmol/L and the five year risk of a major cardiovascular event is 20% using the New Zealand Guidelines. A Microsoft Excel spreadsheet program is available on the Internet for download and can be used to calculate absolute risk (http://www.nzgg.org.nz/library/nzgg-ftp/bloodpressure-calc.exe).

Alternatively, the following tables recommended by others,[1,6] including the National Heart Foundation, can be used to calculate risk of CHD.

Table 2: Patient's risk category associated with risk factors for CHD (modified from ref 1)

Number of risk factors	10-year CHD risk	Risk category
0–1	<10%	low
2	10–19%	moderate
3	20–39%	high
>4	?40%	very high

Table 3: Recommended treatment thresholds by risk category (modified from ref 1)

Risk category	Threshold for treatment	
	LDL-C	TC/HDL-C ratio
Very high	2.5	4
High	3.5	5
Moderate	4	6
Low	5	7

Table 4: Guide for using drugs to lower plasma TC and LDL-C (modified from ref 6)

Risk category	Consider drug treatment*	Target level**
Highest risk Existing ischaemic heart disease Existing extra-coronary vascular disease Diabetes	TC >4.0	
High risk Positive family history of ischaemia heart disease Familial hypercholesterolaemia Hypertension Smoking HDL-C<1.0	TC >6.5	TC $\leq$ 4.0 HDL-C $\geq$ 1.0 LDL-C $\leq$ 2.5 TG $\leq$ 2.0
Lower risk Others (35–75 years old)	TC >7.5	

*It should be emphasised that any lipid lowering is associated with some degree of heart disease prevention. The benefit is maximised by achieving the recommended target levels.[6,7] Consideration for low HDL-C in assessing the need for therapy is included (see below).

**The threshold for treatment is based on assessing risk of cardiovascular disease and Pharmaceutical Benefits Scheme (PBS) guidelines.[7]

Table 4 is probably the easiest one to use by remote health practitioners. The underlying philosophy is for health practitioners to assess the level of absolute risk for individual patients and then to institute appropriate management based on that risk for CHD and level of TC, HDL-C and LDL-C.

Target cholesterol levels

There is a suggestion from the WOSCOPS[30] trial that there may be little gained in primary prevention by lowering total cholesterol much below 5.0 mmol/L. Overall, the trial data suggest that a 1-mmol/L reduction in serum TC sustained over five years will reduce the incidence of non-fatal MI and fatal CHD by 20–25% irrespective of baseline cholesterol and risk.

Serum lipids can be reviewed every six weeks, adjusting dose until desired target achieved then every year.[4]

Follow-up lipid assessment

A number of organisations have recommended that lipid assessment should be performed every five years for those patients at low CHD risk.[1-7] For people with increased CHD risk but TC <5.0 mmol/L, annual assessment is required with promotion of lifestyle measures.

When to refer

Most patients with lipid abnormalities should be managed successfully within the primary care setting. However, referral for specialist care should be considered in:[4]

- Patients who are refractory to treatment after first drug therapy, where secondary causes have been excluded and dietary and lifestyle measures have been tried
- Patients in whom drug therapy is contraindicated or poorly tolerated
- Patients with familial hypercholesterolaemia, to ensure correct identification and screening of relatives including children
- Patients who are pregnant

Special subgroups

Primary prevention in people with diabetes mellitus

Atherosclerosis is the most frequent complication of diabetes, and cardiovascular disease the most common cause of death. The United Kingdom Prospective Diabetes Study (UKPDS) showed that 23% of patients with type 2 diabetes had clinically significant vascular complications at presentation.[39] Serum TC may not differ much from general populations. The LDL-C particles tend to be smaller and more atherogenic in patients with diabetes.

A more common abnormality in type 2 diabetes is an elevation in TG, which is usually associated with low HDL-C. Some patients with type 2 diabetes continue to have high serum TG despite good glycaemic control. Diabetic dyslipidaemia, especially raised TG and low HDL-C, is linked to increased mortality from CHD in both males and females.[5] In the UKPDS potentially modifiable baseline risk factors for cardiovascular disease in patients with type 2 diabetes were LDL-C, HDL-C, hyperglycaemia, HT and smoking.[39]

The numbers of diabetic subjects were too small to reach statistical significance in subgroup analyses of major studies of primary prevention of CHD in diabetic groups.[4] Prospective studies of lipid reduction in people with diabetes are in progress and a meta-analysis is underway. In secondary prevention, however, trials of lipid reduction in diabetics have shown significant reductions in cardiovascular disease in both type 1 and 2 diabetics.[31,32,34]

The long pre-clinical phase in type 2 diabetes with risk factors like dyslipidaemia often means that significant cardiovascular disease is already present but undetected at the time of diagnosis.

It would appear prudent from the above discussion to recommend aggressive lifestyle modification to lose weight, reduce intake of saturated fats, increase consumption of fruits and vegetables, take regular exercise and — where necessary — introduce lipid-lowering drug treatment for primary prevention in diabetic subjects who will mostly be at high risk of CHD. The higher absolute risk for cardiovascular disease in patients with diabetes suggest greater benefit from lipid-lowering therapy than in non-diabetic subjects for a given TC/HDL-C ratio.

Primary prevention for patients with normal TC and LDL-C but low HDL-C

It is well known that low HDL-C is an independent risk factor for CHD. Epidemiological data support the protective effect of high HDL-C regardless

of LDL-C levels.[41] Low HDL-C with normal LDL-C occurs in up to 30% of patients with CHD and may represent a larger proportion of the CHD populations than do those with isolated high LDL-C.[42] A decreasing level of HDL-C is associated with severity of CHD. As yet there is no consensus in guidelines for targeting low HDL-C in patients at increased risk for CHD.

There are two primary prevention studies to date that address the issue of whether lowering HDL-C has an impact on outcome from CHD. These are the Helsinki Heart study (1987)[35], 4000 participants using gemfibrozil 600 mg bd and AFCAPS/TexCAPS (1998)[33] 6605 participants using lovastatin 20–40 mg/d. Both studies showed a significant increase in HDL-C levels (6% lovastatin and 11% for gemfibrozil) with a significant decrease in CHD events over five years of about 34% for lovastatin (NNT = 50) and 37% for gemfibrozil. The AFCAPS/TexCAPS populations were patients at risk for CHD but had normal or mildly elevated TC and LDL-C levels with below average HDL-C levels.

I suggest that these findings support the inclusion of HDL-C levels in risk factor assessment for CHD and suggest the need for reassessment of guidelines regarding pharmacological intervention in patients with normal or mildly elevated TC and LDL-C but low HDL-C levels and who are at increased risk for CHD. The value of statins, with its relatively low risk of side effects compared to earlier treatments for low HDL-C, should add weight to the argument to target HDL-C in the prevention of CHD.

Elevated triglyceride

The mainstay of treatment for elevated triglyceride is physical activity and reduced fat diet. Elevated triglycerides are usually part of a metabolic syndrome where patients tend to have multiple risk factors, including low HDL-C, abnormal glucose tolerance, raised blood pressure and abdominal obesity. These patients are likely to be assessed as high risk.[37]

Fibrates are the drugs of choice in these individuals, but treating the secondary causes (alcohol excess, poorly controlled diabetes and obesity) first is recommended.

TG persistently above 8 mmol/L requires drug therapy because of the risk for pancreatitis. Severe isolated hypertriglyceridemia may be referred to a specialist.

Secondary prevention post-myocardial infarction (MI)

Serum cholesterol and LDL cholesterol are major risk factors for recurrent cardiac events in patients following MI. In patients with acute MI, TC and LDL-C decrease shortly after the onset of the MI. The depression of lipids following MI last an average of six weeks, so it is important to measure lipids within 24 hours of an acute event to give an indication of the TC and HDL-C before the event, otherwise measurements should be delayed until six to 12 weeks after the MI.[40] Dietary modification lowers cholesterol but the changes are small and are poorly maintained as a consequence of limited motivation and non-compliance with stringent dietary restrictions. Recent studies using statins have shown falls in cholesterol of 20–30% and clear benefit in both reductions in vascular events and total mortality.[40]

It could be summarised from the three major studies that, for patients with CHD and TC ≥6.0 mmol/L, drug therapy should be initiated. If TC is between 5.0–6.0 dietary advice is indicated with a follow-up assessment at six to 12 months. If TC is still within this range lipid-lowering drug therapy should then be initiated. If TC is <5.0 mmol/L then dietary advice should be reinforced with yearly follow-up since there is no benefit in groups with TC <5.0 mmol/L in the CARE trial.

To be consistent with the NHF guidelines, for patients with existing CHD and TC >5.0 mmol/L, they should be offered a lipid-lowering agent.

The relative risk reduction observed for pravastatin and simvastatin are similar suggesting a class effect but there have been no trials for atorvastatin, fluvastatin and cerivastatin.

Table 5: Major secondary prevention trials for statins in lowering lipids (modified from reference 39)

		4S		**LIPID**		**CARE**	
		The majority of patients had had an MI at least six months previously or had angina with a positive exercise test.		Patients with established CHD either MI or unstable angina.		Patients with CHD. Study aim to determine whether cholesterol lowering was a benefit for patients with average cholesterol levels.	
Cholesterol range		TC 5.5–8.0 mmol/L		TC 4.0–7.0		TC <6.2	
Mean reduction in cholesterol		TC 28%; LDL-C		TC 18%; LDL-C 25%		TC 20%; LDL-C 28%	
No. Patients		4444		9014		4159	
Treatment groups		Placebo	Simvastatin 20–40 mg/d	Placebo	Pravastatin 40 mg/d	Placebo	Pravastatin 40 mg/d
Trial period (y)		5.4		6.1		5.0	
Total mortality	n	256.0	182.0	633.0	498.0	196.0	180.0
	%	11.5	8.2	14.1	11.0	9.4	8.7
	RRR %	30.0 (p<0.001)		22.0 (ns)		9.0 (ns)	
	ARR %	3.3		3.1		0.7	
	NNT	30.0		32.0		143.0	
CHD mortality	n	189.0	111.0	373.0	287.0	119.0	96.0
	%	8.5	5.0	8.3	6.4	5.7	4.6
	RRR %	42.0 (p<0.001)		24.0 (p<0.001)		20.0 (ns)	
	ARR %	3.5		1.9		1.1	
	NNT	29.0		53.0		91.0	
CHD events	n	622.0	431.0	715.0	557.0	274.0	212.0
	%	28.0	19.0	15.9	12.3	13.2	10.2
	RRR %	34.0 (p<0.001)		24.0 (p<0.001)		24.0 (p=0.003)	
	ARR %	9.0		3.6		3.0	
	NNT	11.0		28.0		33.0	

n = total number of events. ns = not statistically significant.
RRR = relative risk reduction. ARR = absolute risk reduction.
NNT = number needed to treat to prevent one event during the trial period
Event: 4S – CHD death, non-fatal definite or probable MI, silent MI, resuscitated cardiac arrest; CARE – CHD death or symptomatic non-fatal MI; LIPID – CHD death or silent or symptomatic non-fatal MI

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