Focus

Primary prevention of ischaemic heart disease in men with an emphasis on lipid modification

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INTRODUCTION

Ischaemic heart disease is still one of the leading causes of death of men. Advances continue to occur in the management of established ischaemic heart disease, just as there have been major advances in the primary prevention of ischaemic heart disease. In addition, observational studies and completed randomised clinical trials have proven that improved primary prevention is possible, but limits to the prescription of statins is a major issue in New Zealand.

In primary prevention, the assessment of risk and improvements in modifiable risk factors are the cornerstones of treatment. Knowledge of the incremental risks of various factors is important to ensure proper counselling of patients – there should be an emphasis on modification of the most important risk factors if there is to be a major impact on the overall incidence of ischaemic heart disease. This brief review of primary prevention of ischaemic heart disease in men will emphasise lipid modification, and should serve as a useful introduction for those who wish to reference some of the more detailed publications on this topic.

KEY POINTS

- Identify "causal" and "predisposing" risk factors, determine risk status and improve modifiable factors
- In low risk patients, measurement of "conditional" factors is unlikely to make large changes to absolute risk assessment
- Recognise the limitations of guidelines based on the Framingham data
- Recognise that gemfibrozil may be as effective as statins in reducing clinical end points when used in those with average LDL-cholesterol levels with raised triglycerides and low HDL-cholesterol

RISK FACTORS

The Framingham Heart Study has been credited with establishing the importance of various factors in increasing the risk of ischaemic heart disease. Among other large important studies are Prospective Cardiovascular Munster (PROCAM) study in Germany and the Multiple Risk Factor Intervention Trial (MRFIT) in the US. The comprehensive publications resulting from these and other large studies are recommended to those who wish to gain a more in-depth understanding.

The report of a prevention conference of the American Heart Association and the American College of Cardiology divided risk factors into different categories. The findings of epidemiological studies, of basic research, and in some instances the

findings of randomised clinical trials, have led to the identification of "causal risk factors" – these factors are accepted as causing atherosclerotic disease. Other factors described as "predisposing risk factors" seem to worsen the impact of, or may be responsible for, the "causal risk factors". Other identified factors seem to increase the risk of atherosclerotic disease but, to date, the precise risk imparted by these factors, or their independent role has not yet been established – these are referred to as "conditional risk factors".

Causal risk factors

The major independent causal risk factors are: elevated total and LDL-cholesterol, low HDL-cholesterol, diabetes mellitus, smoking, hypertension and advancing age.

Total cholesterol in the MRFIT study had a curvilinear relationship with risk of cardiac events with relative risk rising more markedly when the total cholesterol level increased above 5.0mmol/L. The early large epidemiological studies did not measure low-density lipoprotein (LDL) cholesterol levels but it seems likely that LDL-cholesterol also has a curvilinear relationship to risk.

This relationship is also modified by the presence of other risk factors – the risk being higher for the same LDL-cholesterol level when other causal risk factors are present. The precise relationship between risk and total cholesterol levels seems to be different in Asians, with the risk increasing at lower levels.

Low high-density lipoprotein (HDL) cholesterol levels are also a risk factor. Conversely, high HDL-cholesterol levels are "protective" and the total/HDL-cholesterol or LDL/HDL-cholesterol ratio is a useful tool in clinical practice. In secondary prevention, by definition, the patient is at high risk and treatment should reduce the LDL-cholesterol significantly from pre-treatment values, even when there is a "good" HDL-cholesterol level.

Average LDL-cholesterol levels with low HDL-cholesterol levels and elevated triglyceride levels are often associated with abdominal obesity and diabetes mellitus and higher risk.

levels. If the benefits of gemfibrozil therapy are a "class effect" then other fibrates may be used
- For primary prevention, given the current limitations on use of statins, some patients might be prepared to buy statins. Costs are likely to reduce over the next few years and it would seem unlikely that current limitations on prescriptions of statins for those with other risk factors can remain long term

Since this article was written, the National Cholesterol Education Program (NCEP) Expert Panel in the US released its latest guidelines. These guidelines

Predisposing risk factors

Obesity, abdominal obesity, physical inactivity, family history of coronary disease, ethnicity and possibly psychosocial factors are regarded as predisposing risk factors. These factors may be the cause of causal risk factors or worsen the effects of these risk factors.

Conditional risk factors

This group includes elevated serum triglycerides, small LDL particles, elevated serum homocysteine levels, elevated serum lipoprotein(a), high fibrinogen and high-sensitivity C-reactive protein levels.

incorporate risk stratification based on the Framingham data. The primary goal remains LDL cholesterol lowering below 2.5 mmol/L for secondary prevention, for those with diabetes and for those with multiple risk factors. For those with no risk factors, the target LDL cholesterol is about 4 mmol/L. The guidelines include strategies for management of the "metabolic syndrome" patients who have average LDL cholesterol levels, raised triglycerides and low HDL cholesterol levels. A number of "emerging risk factors" are identified including Lp(a) and homocysteine, but these factors are not part of the Framingham risk calculator.

Future studies may establish the causal link for some of these risk factors and these factors may be incorporated in future guidelines.

Most, but not all, epidemiologic studies suggest that high homocysteine levels increase risk independently of other risk factors. Folic acid supplementation can reduce homocysteine levels. Some are already advocating the routine measurement of homocysteine levels. Hopefully, ongoing prospective trials will establish whether folic acid supplementation will reduce the risk of future coronary disease.

High-sensitivity C-reactive protein is also receiving more interest as it is recognised that inflammation is one of the mechanisms implicated in plaque rupture that leads to acute coronary syndromes. High-sensitive C-reactive protein may thus also prove to be a useful way to help further stratify patients' risk status for future acute cardiac events.

Not all patients with hypertrigly-ceridaemia are at increased risk of future events. One lipid pattern associated with increased risk is the presence of elevated triglyceride levels in those with average LDL-cholesterol levels (with greater numbers of smaller and denser LDL particles) and low HDL-cholesterol levels.

Measurement of apo-lipoprotein B levels has been advocated to help assessment. If apo-lipoprotein B levels are disproportionately elevated compared with calculated LDL-cholesterol levels then this suggests the presence of greater numbers of smaller and denser LDL particles. The authors do not have any personal experience of the routine measurement of apo-lipoprotein B levels.

Lipoprotein(a) in some studies has been associated with increased risk – determination of its role in risk has been affected by the difficulties in measurement of this lipoprotein.

PRIMARY PREVENTION

Trials with lipid modifying agents

Early trials used clofibrate (WHO trial of clofibrate), cholestyramine in the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) and gemfibrozil in the Helsinki Heart Study. These trials showed a reduction in fatal and non-fatal myocardial infarction but concerns were raised about possible increases in non-cardiac deaths. In the Helsinki Heart Study, although LDL-cholesterol was decreased by only 8 per cent and HDL-cholesterol increased by 10 per cent, the per cent reduction in cardiac events (34 per cent) was comparable to the later statin trials.

The West of Scotland Coronary Prevention Study (WOSCOPS) enrolled over 6000 men aged 45–64 years with no history of myocardial infarction, and although it was designed as a primary prevention trial it did include a small proportion of patients with angina or claudication. Patients were randomised to pravastatin or placebo and followed for just under five years.

The mean LDL-cholesterol level at entry was almost 5 mmol/L; this was reduced by 26 per cent with pravastatin therapy. The trial showed a 31 per cent reduction in the combined end point of myocardial infarction and

coronary heart disease deaths. There was a non-significant reduction in the end point of cardiac death alone but an even larger trial is likely to have shown the small reduction to be significant.
The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) study was another large primary prevention trial, this compared lovastatin with placebo and a follow-up of just over five years. It differed from WOSCOPS in a number of ways. Among the differences was the inclusion of women and older participants up to the age of 73 years, a lower mean entry LDL-cholesterol level (3.8 mmol/L), and HDL-cholesterol levels less than 1.16 mmol/L in men and 1.22 mmol/l in women.
With statin therapy there was a 25 per cent reduction in LDL levels, 6 per cent increase in HDL levels and 15 per cent decrease in triglyceride levels. The primary end point (fatal or non-fatal myocardial infarction, unstable angina, sudden cardiac death) was reduced by 37 per cent. Unlike WOSCOPS, this trial included unstable angina as a primary end point.

Post-hoc analysis of trials

No prospective randomised placebo controlled primary prevention trials targeting high risk patients have been completed and published. Studies in diabetics are in progress. Subgroup analysis of the current trials is of interest, even though the findings do not carry the same weight as prospectively designed trials.
In WOSCOPS, subgroup analysis showed that those with isolated hypercholesterolaemia were at low risk. Event rates in the placebo group were low in men with hypercholesterolaemia but no other risk factor: 3.5 per cent for men aged 45–54 years and 5.3 per cent for men aged 55–64 years. In WOSCOPS the total cholesterol levels were as high as 8.0 mmol/L, and greater than 6.5 mmol/L.
Analysis of the placebo group in WOSCOPS also showed the following groups of men had event rates greater than 10 per cent at five years: those with minor ECG abnormalities; those with established vascular disease; smokers; those with HDL-cholesterol levels less than 1.0 mmol/L; and those with a family history of coronary disease.
Subgroup analysis of the Helsinki Heart Study showed that those with LDL/HDL-cholesterol ratio of more than five and elevated triglycerides over 2.3 mmol/L obtained the largest benefit (71 per cent risk reduction). Another analysis from the same study showed that the benefit of gemfibrozil was largely confined to those subjects with a body mass index greater than 26 kg/m2 – the group more likely to have this dyslipidaemic pattern.
In AFCAPS/TexCAPS the lowest two HDL tertile groups had a greater absolute risk of events in the placebo arm compared to the highest tertile. With lovastatin treatment there was a greater than 40 per cent risk reduction in these two tertiles compared to the highest tertile which had a 15 per cent risk reduction. This indicates that statins can produce impressive benefits in those with average LDL-cholesterol levels and low HDL-cholesterol levels.

Selected data from other trials

Some of the findings of the secondary prevention trials can

The findings of the primary prevention and secondary prevention trials have been consistent and show a relative risk reduction of events of 24–37 per cent with LDL-cholesterol reduction of 25–35 per cent. Thus, some of the findings of the secondary prevention trials can be used to support primary prevention strategies.
In the Long Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study there was a 19 per cent reduction in risk of stroke. Similar findings have been reported by other secondary prevention trials. As expected, the absolute risk of

be used to support primary prevention strategies

stroke was much less than the risk of a cardiac event.
A prospective randomised placebo controlled trial of secondary prevention using gemfibrozil 1200mg bd was published in 1999 (the VA-HIT trial). This study included over 2500 men with a HDL-cholesterol level of less than 1.0 mmol/L and a LDL-cholesterol level under 3.6 mmol/L. After a follow-up of over five years there was a 22 per cent relative risk reduction and an absolute reduction of 4.4 per cent in the primary end point of non-fatal myocardial infarction or death from coronary disease.
These results compare very favourably with the statin trials that enrolled patients with higher LDL-cholesterol levels. In this trial there had been no significant change of LDL-cholesterol with gemfi-brozil treatment, but a 6 per cent increase in HDL-cholesterol levels and 31 per cent reduction in triglyceride levels.
The post-CABG trial was an angiographic trial in patients with at least one patent vein graft, and showed that a more aggressive LDL-cholesterol lowering strategy resulted in significant reduction in progression of coronary bypass graft disease. In addition, importantly, the trial also showed reduction in the clinical end point of need for repeat revascularisation. The AVERT study using atorvastatin was more complex but has also been interpreted by many as showing the benefits of more aggressive lipid lowering therapy. Other ongoing secondary prevention trials are also addressing this issue.

Relative and absolute risk reduction

The Helsinki Heart study and the statin trials have shown risk reductions of about 30 per cent. Some subgroups are likely to obtain greater benefits than others, but if one assumes a risk reduction of 30 per cent, than the absolute benefit of treatment will be dependent on the underlying absolute risk without treatment.
Thus, a patient with a 10 per cent risk of a major coronary event over five years would expect this risk will be reduced to 7 per cent by a therapy that reduces relative risk by 30 per cent. Hence the absolute benefit is 3 per cent. The number of patients who need to be treated to prevent one major event over five years is 33 (100 divided by the absolute benefit).
The absolute reduction in the same major events in WOSCOPS was 2.2 per cent and in AFCAPS/TexCAPS 1.6 per cent (numbers to treat 45 and 62, respectively). Interventions in lower risk populations will result in less absolute benefits.

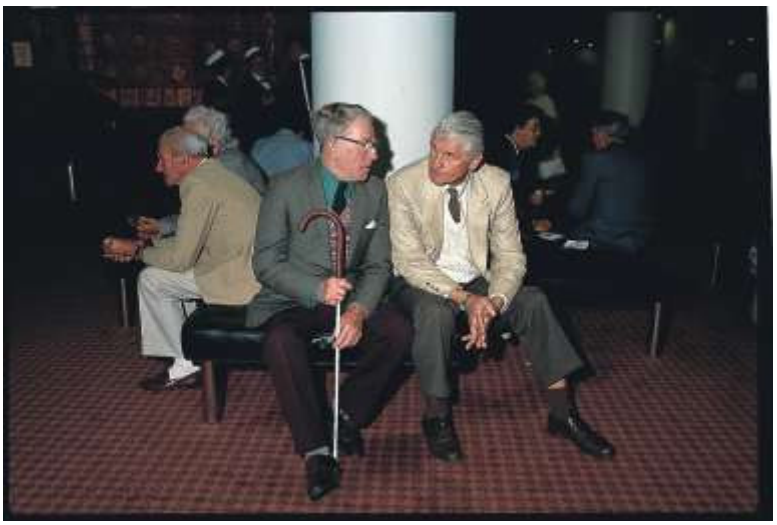
Target LDL-cholesterol levels

WOSCOPS showed no additional clinical benefit with LDL-cholesterol lowering beyond 24 per cent. Subgroup analysis of the Cholesterol and Recurrent Events (CARE) trial, a secondary prevention trial that included patients with lower LDL-cholesterol levels than the other secondary prevention trials, suggested there might be a level of LDL beyond which there was no additional benefit. As stated above, there is evidence from other secondary prevention studies to indicate a more aggressive LDL-cholesterol lowering strategy is beneficial.
The guidelines in the US assume there is significant benefit with lowering of LDL-cholesterol levels down to low levels and recommend, for high risk patients, for primary prevention, lowering of LDL-cholesterol levels to less than 2.6 mmol/L, just as for secondary prevention.
The relationship between coronary event rates and LDL-cholesterol levels is less steep for primary prevention than for secondary prevention. In other words, the degree of absolute benefit for the same per cent reduction in LDL levels is less for primary prevention v secondary prevention.

Cost-effectiveness of drug therapy

Analysis of cost-effectiveness is often based on the findings of randomised clinical trials, and each health system will need to calculate its own cost-effectiveness data. Each health system then has to determine what it is prepared to pay for the potential benefits of therapy.
Whether even the US can afford to treat all those who would meet the inclusion criteria for entry into AFCAPS/TexCAPS remains to be seen. More than 80 per cent of participants in this trial would not have received drug therapy according to current National Cholesterol Education Program guidelines in the US – apparently these guidelines are due for an update. Guidelines developed in the US or even Australia are not necessarily applicable to New Zealand, where the spending on health is less. When restrictions are put in place for use of certain drugs, such as statins, funders should base these decisions on cost-effectiveness and ensure consistency.
The cost-benefit analysis becomes more complex when actual practice differs from the clinical trial. If actual practice becomes more aggressive without a directly proportional increase in absolute benefit (eg, treat to low LDL-cholesterol target) then the cost-benefit analysis calculated from clinical trial data becomes less accurate, but this approach may still be cost-effective. In time, the drug costs may decrease and this might make a particular therapy more cost-effective.
The relationship between dose of statins and per cent LDL-cholesterol reduction is not linear, eg, in one study the "usual" starting dose of a commonly used statin reduced LDL-cholesterol by about 27 per cent but doubling the dose increased this to only 34 per cent. If drug costs increase in direct proportion to the dose, then it is more cost-effective to reduce LDL-cholesterol by 27 per cent than by 34 per cent, but it must be remembered that a 6 per cent fall in total cholesterol is associated with a 12 per cent reduction in cardiovascular events. Thus, the cost-effectiveness of a more aggressive approach is dependent on the increase in absolute benefit obtained.
It is likely the cost of statin therapy will fall once generic statins becomes available and this is likely to see changes in guidelines and practice.

The use of gemfibrozil may be very cost-effective in those who may benefit.



Ace inhibitors in diabetes

The Heart Outcomes Prevention Evaluation (HOPE) study investigated the effects of the ACE-inhibitor ramipril in those with manifest atherosclerotic disease or diabetes with at least one additional risk factor. All participants were older than 55 years and did not have left ventricular dysfunction; over 9000 patients were randomised. The primary end point was the composite of myocardial infarction, stroke or death from cardiovascular causes. The patients were followed for a mean of five years. In this time 14.0 per cent of the ramipril group had an event compared with 17.8 per cent who received placebo. This

benefit is not thought to be due to any blood pressure lowering effect of ramipril.
Post-hoc analysis of trials that used ace inhibitors after myocardial infarction had shown a reduction in myocardial infarction. The HOPE trial has confirmed these findings. The HOPE trial data indicate that only 36 patients need to be treated to prevent one major event.

HYPERTENSION

Hypertension is continuously related to the risk of coronary heart disease with increased risk in more severe hypertensives. The strength of the relationship between hypertension and coronary heart disease is not as steep as the relationship between hypertension and stroke.

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In the Hypertension Optimal Treatment (HOT) trial, there was no significant difference in the outcomes between the three different target groups (diastolic pressure less than or equal to 90, 85 or 80 mmHg) but an analysis of on treatment diastolic pressures indicated that those with lowest diastolic pressures had the lowest event rates.
The purists will remain unconvinced because of the lack of significant benefit in the intention to treat analysis.
In the HOT trial, diabetics assigned to the lowest target pressure group had the lowest event rate, supporting aggressive blood pressure control in this already high risk group. It is also prudent to control hypertension aggressively in those non-diabetics at high risk.
Detailed guidelines on management of hypertension have been updated by the World Health Organization and the International Society of Hypertension (WHO-ISH guidelines) which essentially recommend more aggressive therapy of hypertension. High–normal blood pressure is defined as systolic pressures between 130 and 139 mmHg and diastolic pressures between 85 and 89 mmHg. Borderline hypertension is defined as systolic pressures between 140 and 149 mmHg and diastolic pressures between 90 and 94 mmHg.

DIABETES

Diabetes is a major risk factor for cardiovascular disease. Type II diabetics often have other coexistent risk factors. Diabetics with significant microalbuminuria are at particularly high risk, with a two to threefold increased risk of cardiovascular events. Type II diabetics who are overweight can have average LDL-cholesterol levels, low HDL-cholesterol levels and elevated triglyceride levels – this lipid profile is associated with increased risk – and benefit from fibrate or statin therapy.
The effects of fibrates and statins on the lipid profile is quite different and an area of active research. Combination therapy is advocated for some diabetics. Results of ongoing trials will be of interest. Is combination therapy with fibrates and statins better than aggressive therapy with statins?

SMOKING, DIET and LIFESTYLE

Smoking increases the risk of cardiovascular disease by about twofold in men under the age of 65 years. However, there is a gradation of risk, with higher risk in those who smoke more heavily. That smokers should be encouraged and helped to stop smoking is not in doubt.
Dietary recommendations include reducing fat intake to account for less than 30 per cent of total energy. In addition, recommendations include reducing intake of fats that raise cholesterol; these include saturated fats and trans-fatty acids.
Epidemiological studies suggest that increased intake of fruit, vegetables and fibre is beneficial. Stanol esters can be added to foods and can reduce the absorption of dietary cholesterol.
The Lyon Heart study looked at the effects of a Mediterranean style diet on patients after a myocardial infarction, with very encouraging findings.
Antioxidants have not been shown to reduce risk in prospective controlled trials. Epidemiological evidence also suggests that red wine may be more beneficial but whether this evidence is strong enough to recommend people change the type of wine consumed or begin to consume up to the "recommended maximal daily" alcohol intake must remain contentious until better evidence is forthcoming.
Data obtained from different populations with different dietary and lifestyle factors, as well as a different ethnic mixture, may not be applicable to all populations. However, those who enjoy alcohol in moderation can continue to do so, knowing there is possible benefit.

OBESITY

There is no doubt that obesity (including abdominal obesity) is a major risk factor – the American Heart Association defines this as a causal risk factor rather than as a conditional risk factor. When adjustments for hypertension, diabetes and dyslipidaemia are made, obesity seems not to exert an independent effect in Western populations until the BMI is quite high, over approximately 30 kg/m2.
Because obesity raises blood pressure, raises cholesterol levels, predisposes to diabetes and has other adverse metabolic effects, strategies to target this risk factor remain important. Lowering weight by just 5kg has been shown to reduce blood pressure levels significantly.

FAMILY HISTORY of CORONARY DISEASE

Although family history of coronary disease is undoubtedly a risk factor, it was not included as a major risk factor by the Framingham investigators. They could not determine the degree of independence of this risk factor from other major risk factors. Family history of coronary disease is included in the PROCAM risk calculator.
The taking of a family history remains important. It is likely that a stronger family history will be more significant, eg, onset of manifest ischaemic heart disease in more than one first-degree relative at a younger age is much more

likely to indicate a true genetic predisposition which may be mediated by lipid and non-lipid factors.
The occurrence of early ischaemic heart disease in a first-degree relative who was a heavy smoker or had other major risk factors should not cause the same concern.

ETHNICITY

There has been a rapid increase in the incidence of cardiovascular disease in Asia and these increases are also seen in migrants from Asia to Western countries. The increased incidence seems to be explained by changes in prevalence of causal and predisposing risk factors, rather than being largely due to novel risk factors.
Some of this increased risk relates to smoking, which is common in some Asian countries, while some relates to changes in diet and other lifestyle factors associated with urbanisation and migration. In India, eg, the prevalence of hypertension and of coronary heart disease has doubled and diabetes prevalence is also increasing. Dietary changes have seen an increase in the amount of energy obtained from fat and total cholesterol levels have increased.
Targets for treatment in Indians and other Asians, whether living in Asia or in Western countries, need to be lower. The energy intake from fat should probably be about 20 per cent, the target total cholesterol level as low as 4.4 mmol/L and the target BMI less than 23 kg/m2.

AGE

Advancing age is associated with increased risk, hence most people over the age of 60 years will be at significant absolute risk of events

Advancing age is associated with increased risk, hence, most people over the age of 60 years will be at significant absolute risk of events. According to the New Zealand Heart Foundation Guidelines, nearly all individuals over the age of 75 years will be at high risk for cardiovascular events. It is not clear how we should approach primary prevention with lipid modifying drugs in the elderly who may have other comorbid conditions that will affect their prognosis.

Genetic lipid disorders

A number of genetic lipid disorders are associated with very high risk of future coronary events and aggressive management of these patients is indicated. These patients account for only a small proportion of those admitted with acute cardiac events. Readers should review other literature on this subject for more information.

Assessment of risk status

Different approaches have been adopted by the special societies of different countries. The National Heart Foundation of New Zealand Guidelines are based on the Framingham data and use age, hypertension and the total/HDL-cholesterol ratios as continuous variables. Different risk tables are provided for men and women, for diabetics and non-diabetics, and for smokers and non-smokers.
An American Heart Association/American College of Cardiology scientific statement was issued in 1999 relating to the use of the latest Framingham scoring system. It is emphasised that the Framingham data relating to risk prediction was collected some years ago. The Framingham population may not be the same as other populations in terms of risk. The risk scores may be altered by predisposing and conditional risk factors.

The PROCAM study group has derived its own risk calculator that can be accessed at the website of the International Task Force for the Prevention of Coronary Heart Disease. The PROCAM study group's risk assessment is not directly comparable to that of Framingham, since the definition of major cardiac events differed. In essence, the Framingham group included more "softer" end points such as ECG evidence of myocardial infarction, thus the predicted event rates are higher.
More simple assessment of risk by counting the number of major risk factors will be much less accurate since this method does not take into account higher risk with, eg, more severe degrees of dyslipidaemia.

Aspirin for primary prevention

The Primary Prevention Trial recently published in the Lancet showed a trend for benefit with low dose aspirin for the combined primary end point of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. This non-blinded trial had recruited patients with at least one risk factor. The HOT trial also investigated the effects of low-dose aspirin and found benefit and recommended use of aspirin, provided hypertension was well-controlled.

INDIVIDUAL LIPID MANAGEMENT

A full history and examination is required to assess for manifest atherosclerotic disease, for causal and conditional risk factors, for other comorbid conditions, and for possible genetic lipid disorder.
The diet has to also be assessed and appropriate advice relating to this and other risk factors provided.
The National Heart Foundation Guidelines recommend a minimum of two lipid measurements done within two weeks in case there is significant biological and analytical variation in the result. One of these tests should be fasting. A third measurement may be necessary if the total cholesterol varies by more than 1 mmol/L and the HDL by more than 0.25 mmol/L.
The patient's risk is assessed; assessment is made for possible secondary causes of dyslipidaemia including full routine biochemistry, haematology and thyroid tests.
The guidelines recommend "intensive" dietary advice which includes detailed dietary assessment and regular dietitian follow-up for those with total cholesterol levels above 5.5 mmol/L and for those at >20 per cent five-year risk of major events (like many guidelines, this may reflect the ideal practice rather than what can be achieved in most areas). "Specific dietary advice" by a trained health professional is recommended for most, except those with total/HDL ratio less than 5.5.
The goals of treatment are total cholesterol of 3.0–5.0 mmol/L, HDL-cholesterol above 1.0 mmol/L, total/HDL-cholesterol ratio of less than 4.5 and triglycerides of less than 2.0 mmol/L.
Presumably, when updated, the New Zealand Heart Foundation Lipid Guidelines will alter some of the target levels. For primary prevention of high risk patients, LDL-cholesterol of less than 2.6 mmol/L and for other patients LDL-cholesterol less than 3.5 mmol/L may be a reasonable target, based on recommendations of other groups.
Current Pharmac criteria state that those patients with manifest atherosclerotic disease qualify for use of statins, provided total cholesterol levels exceed defined limits. For primary prevention, diabetics with significant microalbuminuria and those with a genetic lipid disorder with total cholesterol levels over 6 mmol/L qualify for use of subsidised statins. For others, only those with total cholesterol over 9 mmol/L qualify for subsidised statin therapy. Yet many guidelines, including the New Zealand Heart Foundation Lipid Guidelines, would recommend drug treatment for groups of patients who do not meet current Pharmac criteria for use of subsidised statins.

Given the findings of the Helsinki Heart Study and the VA-HIT study it would be reasonable to use gemfibrozil for primary prevention in those with average LDL-cholesterol levels, low HDL-cholesterol levels, particularly if triglyceride levels are elevated. Cholestyramine could be tried in other patients with hypercholesterolaemia and continued if the drug is tolerated – it is best to start at a low dosage and increase progressively. However, the LDL-cholesterol reduction with chol-estyramine alone may not be sufficient in patients who cannot tolerate high doses.
Some patients may wish to consider buying a statin to improve the lipid profile. The cost of this treatment may not be that different from a good life insurance policy. These patients may only be able to make this decision after full explanation of the findings of the trials. Measurement of conditional risk factors may be of some help in further risk stratification, recognising the current uncertainties regarding these risk factors.

Some patients may wish to consider buying a statin to improve the lipid profile

It would be reasonable to emphasise that the event rates in the treatment and placebo arm of the statin trials seemed to continue to diverge and thus it is expected the long term benefits of statin therapy will exceed those described in the statin trials, which ended after about five years. The benefits of statin therapy are greater if one includes other end points such as occurrence of unstable angina and not just major coronary events (death and non-fatal myocardial infarction).
If a patient decides to buy a statin for primary prevention, and if one believes that all statins will produce the described benefits, it might be reasonable to use the cheapest statin to reduce LDL-cholesterol levels by about 25 per cent to obtain the most cost-effective benefit. A more aggressive approach with use of higher doses of statins may not reduce LDL-cholesterol levels a lot more in some patients and individual decisions will need to be made about whether this is cost-effective.
It is possible that within a few years the cost of statins will reduce once generic statins come on the market and this should herald ever more widespread use of statins for primary prevention. This may also result in further debate about whether all statins have the same clinical effect regardless of some of the differences in other properties of statins.

ASSESSMENT for SUBCLINICAL ISCHAEMIA

Intuitively, it seems reasonable to search for subclinical evidence for atherosclerotic disease including subclinical ischaemic heart disease to try to identify those patients who might obtain even more benefit from primary prevention strategies.
The use of any screening test requires one to be familiar with Bayesian principles. If the pre-test probability is low, a positive test usually will not change the absolute risk of the abnormality being present substantially. Similarly, in those with a high pre-test probability a negative test does not markedly reduce chances of disease being present.
Thus, the usefulness of any screening test is determined by the prevalence of the disease in the population being studied (the pre-test probability), and the sensitivity and specificity of the test. Whether the false positive rate is acceptable when screening for a particular condition is dependent on many factors, such as the accuracy of the test, the severity of the condition being screened for, the availability of effective and accessible therapy for the condition, and cost considerations.
Exercise stress testing is most reliable, if used in a low risk population, for excluding advanced coronary disease, ie, a negative test can be relied upon more than a positive test in this situation. However, since most acute coronary events occur due to rupture of minor coronary plaques, a negative stress test cannot be used to decide against use of primary prevention

strategies.
New measures of coronary plaque burden are being investigated. Two examples are measurement of carotid artery atherosclerosis by sonography and electron-beam computed tomography to measure directly the calcium content of coronary arteries – the calcium content measured by this technique correlates with the extent of atherosclerosis.
Further publications more convincingly showing the advantages, or otherwise, of use of tests to detect subclinical atherosclerotic disease are likely to be forthcoming, but to date are not yet recommended for routine use.

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