Lipid disorders

the challenge of patient management

Lipid abnormalities play a key role in the development of coronary heart disease (CHD). Lipid-lowering therapy reduces the risk of a future coronary event in those with or without prior CHD and reduces the risk of stroke in those with prior CHD. Statins are the first choice in drug therapy for a predominant cholesterol problem, whereas for a predominant triglyceride problem fibrates are still the first option for treatment.

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Over the last 30 years there have been important changes in the treatment of patients with lipid disorders. This is for at least three key reasons:

- there are new and improved treatments
- there is evidence testifying to the benefit and safety of treatment
- there are new economic imperatives.

Although many factors are involved in the genesis of atherosclerosis and coronary heart disease (CHD), it is accepted that lipid abnormalities play a key role (Figures 1 and 2). Elevated low density lipoprotein (LDL) cholesterol (and hence total cholesterol) is a key causal factor. High density lipoprotein (HDL) cholesterol functions in a protective role. Triglycerides, usually inversely related to the HDL reading, are important but occupy a more equivocal position in cardiovascular disease epidemiology (see below).

Lipid therapy is clinically effective

There is abundant evidence from gold-standard clinical trials that statin drugs (and to a lesser extent fibrates) significantly reduce the risk of a future coronary event or stroke and the risk of dying by 20 to 30% in patients with prior CHD, whether patients have elevated or just average cholesterol readings. Lipid-lowering therapy also significantly reduces the risk of future coronary events in patients without prior CHD, but any impact on stroke risk or life expectancy in this group has been difficult to demonstrate, largely for statistical and methodological reasons.[1] While side effects undoubtedly occur at a low rate with this treatment, randomised placebo-controlled trials testify to the safety of drug therapy. Treatment is not associated with any change in noncardiovascular mortality.

Lipid therapy is not equally cost-effective in every situation. This can be indirectly examined as the number needed to be treated (NNT) to prevent one vascular event during a typical five-year trial (Figure 3). In those with prior CHD (i.e. secondary prevention), the NNT to prevent one coronary event is quite modest and compares

IN SUMMARY

- **Blood lipids are important factors in coronary heart disease.**
- **Lipid therapy safely and effectively reduces coronary risk and increases life expectancy.**
- **Lipids assume their greatest importance in those patients with prior CHD or in those with multiple risk factors.**
- **Statins are the first choice in drug selection for a predominant cholesterol problem.**
- **Fibrates are the first choice in drug selection for a predominant triglyceride problem.**

very favourably with the higher NNT to prevent a stroke using antihypertensive therapy. In those without prior CHD (i.e. primary prevention), NNT to prevent one coronary event is substantially greater and it is here that we are currently working to define those at high coronary risk (i.e. risk stratification).

Lipid-lowering therapy in those with prior CHD also reduces the risk of stroke (Figure 4). In this role the treatment appears to be as cost-effective as in the single comparison made with antihypertensive therapy. The data indicate no major impact on stroke risk in those without prior CHD.

Defining those at high risk

Originally the focus of lipid-lowering therapy was on lipid readings. Those with very high readings received therapy, others did not. The focus has now shifted to treating those at high future coronary risk. Clearly, this is any patient with prior CHD (and probably other forms of atherosclerotic vascular disease) or any patient with diabetes.[2] Unless these patients have unusually favourable lipid and lipoprotein levels, most of them will need lipid therapy, consisting of dietary advice and appropriately chosen drugs (see below). There may also be an important role for statins in the early hours of an acute coronary syndrome, but this remains under investigation.[3]

The new challenge is to stratify coronary risk in patients who do not have prior CHD or diabetes and thus ultimately to decide who will be the most likely to benefit from lipid therapy. This is the basis of both the lipid management guidelines from the National Heart Foundation (currently under review) and subsidy guidelines for prescribing on the Pharmaceutical Benefit Scheme (PBS). The PBS guidelines, in themselves far from ideal (they do not take into account cigarette smoking, for example), require practitioners to grade patients according to their degree of future coronary risk. Those at low absolute coronary risk (with, say, a borderline lipid value and no other risk factors) are more cost-effectively managed with diet and lifestyle advice. Those at unacceptably high coronary risk (with, say, an additional risk factor) will be prescribed lipid-lowering drugs in addition to diet and lifestyle advice.

Unlike the situation in Europe, the USA or New Zealand, Australian practitioners are not required to perform a formal calculation of absolute coronary risk. There are major pitfalls and assumptions in making these calculations. Perhaps we have been wise not to move down this path yet, but this point remains controversial.

New predictors

Other measurements such as lipoprotein (a), homocysteine and C-reactive protein are potentially useful in risk stratification. Although these are markers of increased coronary risk, their utility in deciding who should receive lipid-lowering therapy is unresolved.

C-reactive protein, a marker of inflammation, is particularly interesting because it may serve to indicate a patient who has unstable atheromatous plaque, possibly someone in need of lipid therapy.[4] C-reactive protein levels are reduced by intake of any of the statin drugs, and this may be beneficial. But would one deny lipid therapy to a patient who does not have elevated C-reactive protein levels who otherwise is rated at high coronary risk? I think not.

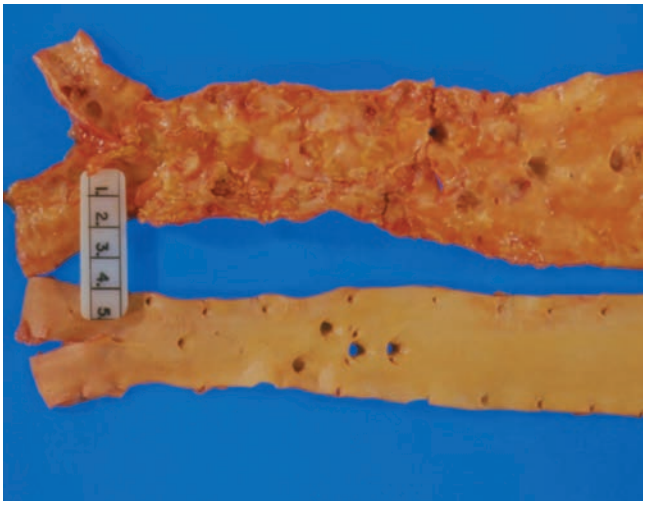

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Figure 1. Atherosclerosis. Comparison between a healthy aorta (bottom) and one showing several plaques (yellow–white) of atheroma. It is accepted that lipid abnormalities play a key role in atherosclerosis and coronary heart disease.

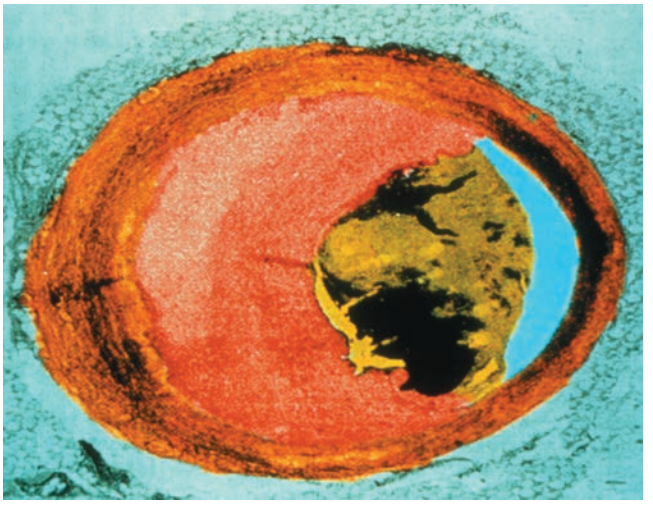

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Figure 2. Coloured cross-section through a coronary artery showing atherosclerosis. The artery wall is red, hyperplastic cells are pink and fatty plaque is yellow. The markedly reduced lumen is seen as the blue area.

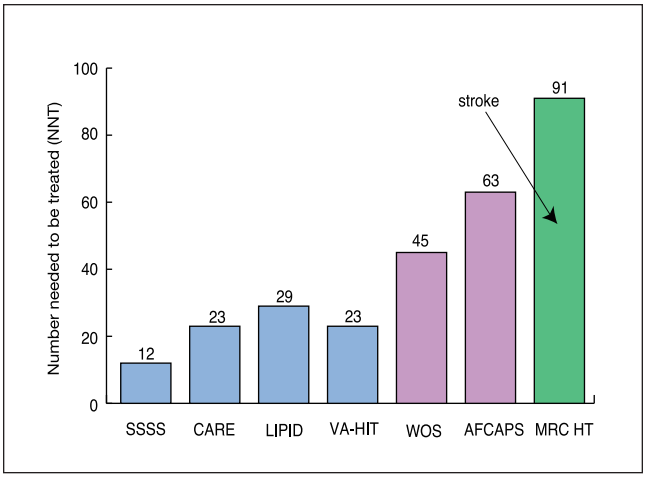

Figure 3. Number of patients needed to be treated over five years to prevent one coronary event in a series of randomised placebo-controlled trials. The four trials to the left are examples of secondary heart disease prevention. The next two are examples of primary heart disease prevention. The impact of antihypertensive therapy on stroke events is shown at the extreme right (only one example has been selected). These values were calculated by the author from the original published results.

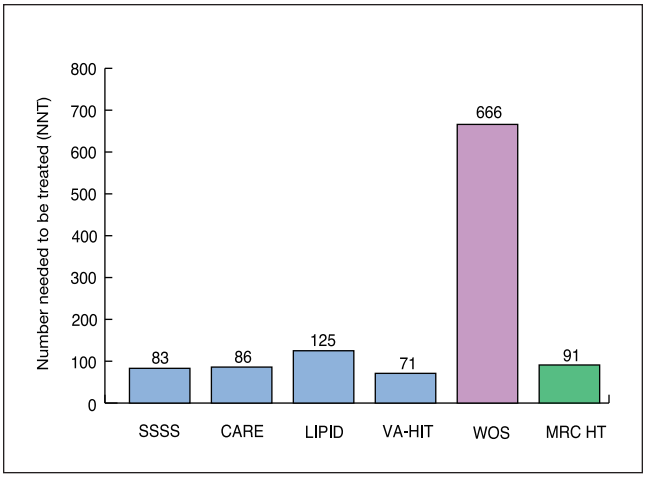

Figure 4. Number of patients needed to be treated over five years to prevent one stroke event in a series of randomised placebo-controlled trials. The four trials to the left are examples of secondary heart disease prevention. The next is an example of primary heart disease prevention. The impact of antihypertensive therapy on stroke events is shown at the extreme right (only one example has been selected). These values were calculated by the author from the original published results.

How should we handle the triglyceride issue?

If patients have highly elevated triglycerides (say, exceeding 8 to 10 mmol/L), they are also at risk of acute pancreatitis and need specific lipid management. For less severely affected patients, definitive answers have yet to be forthcoming from controlled intervention trials.

Studies of CHD in the elderly population of Dubbo, NSW allow some insight into the difficult question of cholesterol–triglyceride–HDL inter-relationships. An elderly population of almost 2800 senior citizens were stratified by their triglyceride and HDL readings into three groups:

- low triglyceride–high HDL (triglyceride <1.20 mmol/L; HDL cholesterol >1.33 mmol/L in men, >1.56 mmol/L in women)
- high triglyceride–low HDL (triglycerides >1.80 mmol/L; HDL cholesterol <1.06 mmol/L in men, <1.24 mmol/L in women)
- the remainder (62% of the study population).

The rate of acute myocardial infarction over 12 years' follow up was 6.8/100 in the low triglyceride–high HDL group and increased almost threefold to 17.3/100 in the high triglyceride–low HDL group. LDL cholesterol was predictive of acute myocardial infarction in the population generally, but more highly so in the high triglyceride–low HDL grouping.[5]

Who were the patients in this high triglyceride–low HDL group? They were the individuals who also had high prevalence of central obesity, diabetes and hypertension. In other words, they manifested the metabolic syndrome. If there is a practical message in regard to the triglyceride–HDL issue, it is that patients with the metabolic syndrome deserve special attention to their cholesterol problems, as well as specific management of their high triglyceride–low HDL abnormality. Recent clinical trials with fibrates attest to the merit of triglyceride reduction and HDL raising.[6]

Barriers to implementation

Research conducted in Australia and overseas indicates that patients are not receiving lipid-lowering therapy according to local guidelines, especially those patients with prior CHD. Commencement of statin drugs, where appropriate, may lead to more patients receiving and remaining on long-term therapy.[3]

In a recent study, 32,384 patients newly prescribed a lipid-lowering drug over one month were monitored for compliance. Ninety-two per cent of these patients had been prescribed statin drugs. Within six to seven months, 30% had discontinued treatment.[7] This represents a lost opportunity for proven heart disease prevention.

Treatment choices

Treatment choices have not changed substantially over recent years.[8] All

patients should receive diet and lifestyle advice. Drug therapy should be prescribed according to current PBS guidelines.

For a predominant cholesterol problem

If the goal of therapy is LDL cholesterol reduction in a patient with a predominant cholesterol problem (reduction to 2.6 mmol/L in a patient with prior CHD, 3 to 3.5 mmol/L in others), then a statin drug will be first choice. Evidence of clinical benefit is strongest with simvastatin (Lipex, Zocor) and pravastatin (Pravachol). However, many authorities hold the view that benefits observed with statins are a class effect and these are likely to be achieved with any statin drug, provided substantial LDL reduction occurs.

For a predominant triglyceride problem

If the goal of treatment is improvement in a triglyceride–HDL abnormality in a patient with a predominant triglyceride problem, then fibrate drugs such as gemfibrozil (or fenofibrate, which is not yet available in Australia) will be the first choice. This would be in preference to using a statin drug.

An alternative to fibrates would be the use of a high dose of omega-3 fatty acid derived from fish oil (e.g. Maxepa).

For combined hyperlipidaemia

Patients with 'combined hyperlipidaemia' remain a serious challenge, as no single drug will correct this problem in every case. If triglycerides are moderately elevated (say up to 5 mmol/L), then statins are still appropriate. If triglycerides are more highly elevated, fibrates would be first choice, irrespective of the cholesterol reading. Combination therapy should be reserved for patients at very high coronary risk. This might be a statin drug plus an omega-3 fatty acid. Combination therapy of statin and gemfibrozil should be approached with extreme caution and manufacturers' official product information should be strictly followed.

The future

As we set more aggressive but justified LDL cholesterol goals, we will generate a cohort of patients who will be disappointed with their outcomes. We should be ready to reassure such patients that proportionately large reductions in LDL cholesterol are still highly beneficial. In the future we will see the availability of newer and more potent statin drugs, but gains from this new therapy will be at the margins.

There is a need to consider dose titration with statin drugs. Every doubling in the dose of a statin drug will achieve an additional 6% reduction in LDL cholesterol. Hence, to achieve an additional 18% reduction would require an eightfold increase in the dose of statin, from say 10 up to 80 mg/day (Figure 5). The addition of plant sterols to the diet, say 20 to 25 g/day of plant sterol-enriched margarine, would offer an LDL reduction equivalent to a fourfold increase in dose of statin. Despite recent adverse publicity, the use of plant sterols is still regarded

Consultant's comment

Rational prescribing is based on evidence of optimal balance between benefits on the one hand, and risks and costs on the other. The case of lipid-lowering highlights two important issues in preventive drug therapy: drug safety and cost-effectiveness.

Drug safety

In preventive therapy, because many healthy individuals need to be treated for long periods to prevent disease in a few, even low risks of adverse events associated with a preventive medication may be sufficient to tip the balance in favour of harm over benefit. This must be borne in mind when starting patients on preventive medications.

Cost-effectiveness

The importance of cost-effectiveness is underscored by the fact that preventive medications now cost more to the Pharmaceutical Benefits Scheme than curative medications. HMG-CoA reductase inhibitors (statins) alone account for approximately $600 million annually.

There are two basic considerations to cost-effectiveness: absolute risk reduction (effectiveness) and cost.

Absolute risk reduction is a function of relative risk reduction and pretreatment risk. Those patients with high pretreatment risk stand to benefit more from preventive interventions, and hence are those for whom cost-effectiveness is greater. It is for this reason that secondary prevention is generally cost-effective, while in the primary preventive setting, targeting high-risk individuals is the key. It is imperative to realise that risk for cardiovascular disease is conferred by multiple risk factors. Accordingly, risk stratification and treatment should always address a range of risk factors. For example, it may be more cost-effective to treat a hypertensive, smoking individual with slightly elevated LDL-cholesterol than another with much higher LDL-cholesterol in the absence of other risk factors.

Cost is the other determinant of cost-effectiveness, and where two (or more) medications are of equal efficacy, in the absence of other indications or contraindications, clinicians should prescribe the cheaper alternative.

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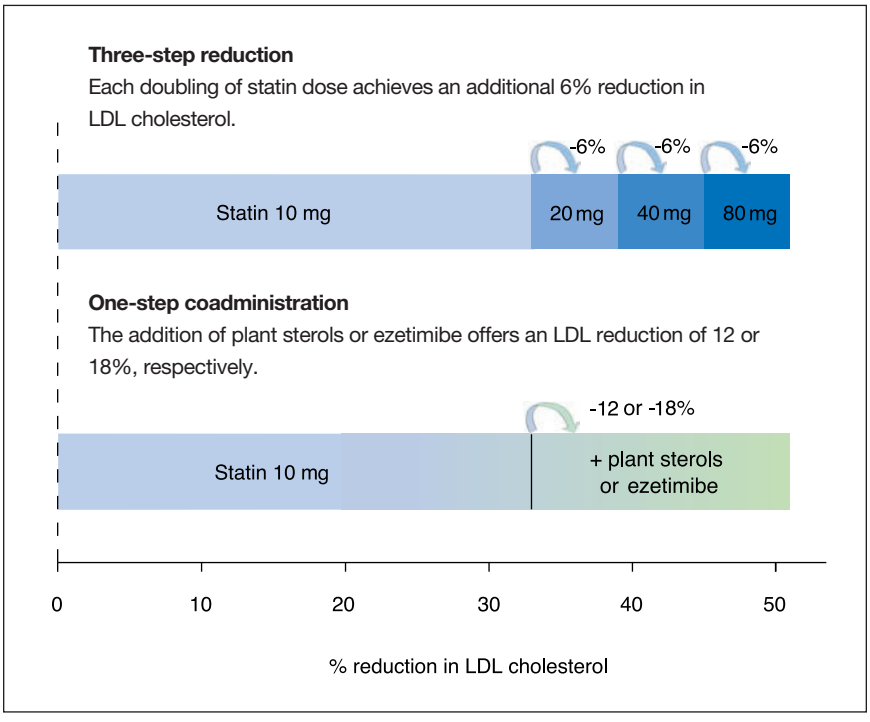

Figure 5. The effect on LDL cholesterol of a three-step dose titration with a statin drug versus the effect of a one-step coadministration of other treatment.

as generally safe. In future years, we might prescribe a second drug known as ezetimibe (not yet available in Australia), which reduces cholesterol absorption, and this might achieve an effect equivalent to an eightfold increase in statin dose.

Conclusions

There is a relatively expensive price tag attached to lipid-lowering therapy; however, this appears to be fully justified. Lipid therapy is effective and safe, but the challenge is to offer the treatment in a cost-effective manner. This may ultimately mean that low risk patients with lipid abnormalities do not receive drug therapy, while patients at high coronary risk must continue to do so. MT

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