Cardiovascular disease and lipid management in New Zealand: progress at last!

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Background

Epidemiological studies in the 1950s and 1960s established the crucial association between raised total cholesterol and the development of ischaemic heart disease.[1] The Framingham study investigators coined the term 'risk factor'.[2] Initial attempts to demonstrate reductions in the rate of ischaemic heart disease through cholesterol reduction were hampered by the limited potency of the then available drugs and a relatively high level of patient side effects. Nonetheless, the Lipid Research Clinics Coronary Primary Prevention Trial[3] using cholestyramine and the Helsinki Heart Study[4] using gemfibrozil demonstrated a reduction in cardiac events in 'high risk' populations. The Coronary Drug Project[5] using high dose nicotinic acid, also demonstrated benefit in patients with established ischaemic heart disease, although it took sixteen years for a statistically significant mortality end-point to emerge.[6]

The development of the potent and safe 'statin' drugs allowed efficacy, angiographic and endpoint outcome studies to be initiated. The 'angiographic' trials[7,8] typically showed only minimal 'regression' of coronary atheroma, yet a significant decrease in the number of cardiovascular events for patients randomised to statin drugs. These observations consolidated the concept of endothelial stabilisation, resulting in reduced atheromatous plaque rupture and acute coronary syndromes.[9,10]

Five major placebo-controlled statin trials were completed in the 1990s. Three were in populations with known coronary disease: the Scandinavian Simvastatin Survival Study (4S)[11] using simvastatin, the Cholesterol and Recurrent Events (CARE) trial[12] using pravastatin, and the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study.[13] Two trials were in populations without known coronary disease: the West of Scotland Coronary Prevention Study (WOSCOPS)[14] using pravastatin and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)[15] using lovastatin. All five trials showed similar relative reductions in vascular endpoints of myocardial infarction, stroke or cardiac death of approximately 30% over five years. After the presentation of 4S,[11] the 1996 New Zealand Lipid Guidelines[16] were formulated and then published and have been a valuable tool to help clinicians identify high-risk subjects in whom cholesterol reduction would confer cardiovascular benefit. Around the same time the Pharmacology Management Agency (PHARMAC) established its guidelines for statin approval, and these remain substantially unchanged in 2002.

More recent publications

Following the publication of the 1996 Guidelines,[16] the CARE,[12] LIPID[13] and AFCAPS/TexCAPS[15] studies were published. CARE and LIPID demonstrated the benefit of statin therapy in patients with known ischaemic heart disease and cholesterol levels much lower than for 4S (>4mmol/L).[12,13] AFCAPS/TexCAPS extended the benefit of statins to a low-risk population with a total mean cholesterol of 5.7mmol/L and a relatively low mean high-density lipoprotein (HDL) cholesterol of 0.96mmol/L.[15]

Other major studies have also been published since the 1996 New Zealand Lipid Guidelines.[16] The Post Coronary Artery Bypass Graft (CABG) trialists study[17] using lovastatin (and cholestyramine), and the Aggressive Lipid Lowering with Atorvastatin versus Revascularisation Treatments (AVERT) trial[18] enrolled patients with prior revascularisation with CABG surgery or percutaneous coronary intervention (PCI) and randomised them to vigorous versus standard lipid management, as a major part of the trials. Both trials demonstrated that vigorous cholesterol lowering treatment to a level below 4mmol/L[18] or a low-density lipoprotein (LDL) cholesterol well below the 2001 United States National Cholesterol Education Program (NCEP) Adult Treatment Panel 3 (ATPIII) guidelines of 2.6mmol/L,[19] resulted in greater clinical benefit than for less stringent lipid targets. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study,[20] using 80 mg atorvastatin daily, demonstrated that treating patients with an acute coronary syndrome with a statin between 24 and 96 hours following hospital presentation was not only safe, but also beneficial for reducing vascular events by the fourth month of therapy. The recommendation of the 1996 Guidelines to delay statin treatment for 3-6 months in order to assess the effect of diet and lifestyle change,[16,21] is thus obsolete. Correspondingly the inclusion of this stand-down period in the PHARMAC approval system for statins up to date, has been against medical evidence, and has compounded short and long-term compliance treatment issues. Endpoint fibrate studies have also been published since 1996. The Veterans Affairs High-Density Lipoprotein Cholesterol intervention Trial (VAHIT)[22] using gemfibrozil and the Bezafibrate Infarction Prevention (BIP)[23] trials have demonstrated that LDL cholesterol reduction by statins is not the only way of reducing vascular events. In an ischaemic, dyslipidaemic population whose principal problem was low HDL cholesterol and a raised triglyceride level, fibrate drugs significantly reduced the risk of myocardial infarction, stroke and death.[22,23]

The heart protection study

By far the largest statin trial, the Heart Protection Study, has recently been presented at the American Heart Association Scientific Meeting in November 2001 in Anaheim, California[24,25] and its results disseminated to the medical community on www.hpsinfo.org. 20 536 British subjects were enrolled: 13 379 with coronary disease and 7157 (35%) without overt coronary disease. Of these 'non-coronary' subjects, 1822 had cerebrovascular disease, 2185 peripheral vascular disease, and 3150 were selected because they were at 'high risk' of developing vascular disease, being treated for diabetes mellitus (n=2913) or hypertension (n=237). Patients with a total cholesterol of 3.5mmol/L and above were randomised to

simvastatin 40mg daily or placebo. The 2 x 2 factorial design of the study also randomised patients to 600mg Vitamin E, 250 mg Vitamin C and 20 mg beta-carotene daily versus placebo, but the addition of these supplementary antioxidant vitamins had no beneficial effects. However the simvastatin therapy was extremely well tolerated and safe, resulting in a 24% risk reduction of vascular events, including myocardial infarction, stroke and death. This study has provided a major extension to our statin knowledge. It indicates that patients aged between 40 and 80 years, with either coronary, cerebrovascular or peripheral vascular disease, or those at high risk of developing vascular disease due to pre-existing diabetes mellitus, and with cholesterol levels of 3.5mmol/L or above, would benefit from a statin drug.[25] Those with pre-existing hypertension may also benefit, although only a small number of subjects (n=237) were enrolled in HPS.[25] Further, as with all of the statin trials, the outcome differences between the treated and placebo groups continued to increase with time, indicating that an even larger benefit for those patients being treated with a statin would probably be seen beyond the five years of the trial. The study lays to rest many controversies of the last decade. Simvastatin was as effective in females as in males, and was beneficial in old and young subjects. Most importantly it showed that there is no level of cholesterol at which benefit is not seen and there was no suggestion of a threshold level. Patients with low baseline LDL levels (less than the current NCEP target) achieved equal relative risk reduction to those with higher levels. Benefit was seen in the diabetic cohort, those with cerebrovascular disease, and those with peripheral vascular disease. Patients with renal disease seemed to benefit relatively more than other groups.[25]

Progress at last

It has been abundantly clear to many that the clinical management of patients with vascular disease and those at high risk of developing vascular disease in New Zealand has needed to move forward in line with these scientific studies. Fortunately the Heart Foundation, individual clinicians and PHARMAC, under the auspices of the Guidelines Group, are currently addressing this need.

1. Perhaps the most long overdue change is with PHARMAC.[26-28] The impact of PHARMAC has to date had a major, negative effect on good lipid management in New Zealand.[29-35] It took PHARMAC 30 months to respond to the landmark 4S study, before they lowered the cholesterol level at which patients could receive statin therapy from an unacceptably high value of 7 mmol/L to 6 mmol/L.[36] Compounding this, the only fully funded statin available at that stage was fluvastatin.[37,38] The effect on clinical care for high risk New Zealand patients was recognised by clinicians[30-35] and was a contributory factor for the sub-optimal lipid control described in several audits.[39,40] Despite medical commentary,[41,42] PHARMAC failed to adjust to these data from randomised clinical trials, preferring instead to claim success with their policies by letter[43-45] and through their annual reports.[46,47] For many years, the cholesterol level at which patients with ischaemic heart disease could receive a subsidy for a statin was 5.5mmol/L or 4.5mmol/L for those with a previous CABG or PCI.[21] From 1st April 2002, through a pricing arrangement with Merck, Sharp and Dohme, simvastatin became available at a fully funded level without need for special approval and without any scrutiny of baseline cholesterol level. This will allow clinicians to implement the clinical message of the HPS Study, viz: that there should be no cholesterol value set as an entry point for therapy in patients with ischaemic heart disease or at high risk for cardiovascular disease. While this is a welcome change, it carries concerns. Fluvastatin is immediately bench marked against simvastatin and will carry a considerable part charge and within two years the same may happen with atorvastatin. Withdrawal of these statins is a possibility in that circumstance leaving New Zealand with a sole statin agent on the market. That would compromise the care of many subgroups of patients. Furthermore it creates an impossible environment for the fund listing of the newer so called 'super-statins'.
2. The 1996 New Zealand Lipid Guidelines correspondingly have been long due for an update and the reconvening of a group to do this is welcomed. The guidelines will undoubtedly reflect the available clinical trial data and it is assumed they will endorse more vigorous lipid management, in terms of total and LDL cholesterol reduction,[48] as well as focussing attention on patients with low HDL and high triglyceride levels.[48-50] The more important task, however, will be the difficult process of ensuring that the guidelines are implemented in primary and secondary practice, that priority treatment is applied to those with highest risk and that lower risk patients are not given statin treatment based simply on laboratory values of cholesterol.
3. It follows that clinicians will need to become guideline 'wise' and practice accordingly, adopting the messages from scientific trials more effectively than has been reported to date.[39,51-53]
4. The issue of patient compliance needs to be addressed both in New Zealand and overseas. Methods of improving patients' uptake of medication must be explored,[54,55] and include assessments of how the patients understand their illness.[56,57] In the future, large numbers of patients and high-risk individuals will be prescribed lipid modifying medicines over prolonged periods of time, and will only gain a benefit if they comply with treatment.

In summary, we are now experiencing a paradigm shift in our understanding of the role of lipid management and cardiovascular disease. There are currently approximately 120 000 New Zealanders receiving lipid-modifying agents.[47,58] A figure closer to 400 000 within five years would vastly improve patient outcomes for cardiovascular disease, the commonest cause of death and major morbidity in New Zealand.[59] The impending changes to access if coupled with utilisation of the soon to be available guidelines will allow most high-risk patients to be more effectively treated. All doctors have a responsibility to use this clinical resource efficiently and wisely.

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