Statins and cardiovascular disease — major therapeutic advances but are we seizing the moment?

See page 1119 for the article to which this Editorial refers

Sexy it is not, but cholesterol has been a remarkable cardiovascular success story over the past 6 to 7 years. It feels like only yesterday when experts were assuring us that cholesterol was only a bit player in the cardiovascular epidemic, and yet reassuringly those who believed that (with effective therapeutic agents, and, as importantly, properly constructed and powered trials) the importance of cholesterol reduction could be clearly demonstrated have been more than vindicated. The major studies published between 1994–1995 (4S[1] and WOSCOPS[2]) and which looked at secondary and then primary prevention of cardiovascular events using effective cholesterol lowering therapy, not alone demonstrated a significant benefit from such a treatment approach, but did it with sufficient zeros after the P that there was little question whatever about that benefit.

As questions were answered, others were raised. Clearly reduction of elevated cholesterol/LDL-C was of prognostic benefit, but why do so many people with ‘average’ cholesterol get premature coronary artery disease? So another large well designed study (CARE)[3], with long follow-up of patients with prior myocardial infarction, but with average cholesterol levels randomized to placebo or pravastatin — and, lo and behold — despite the relative normality of the cholesterol, those randomized to treatment gain the same long-term prognostic benefit (again lots of zeros) as those with elevated cholesterol in previous studies. The LIPID study group[4] has subsequently confirmed similar significant benefit from long-term cholesterol reduction with pravastatin in similar patients who had a wide range of baseline cholesterol levels. And so the message begins to unfold — if one develops premature coronary artery disease, ones cholesterol/LDL-C is likely too high, irrespective of what it is. Begs the question what is a normal cholesterol in the face of coronary artery disease? Perhaps even more interesting with reference to this point is the findings of the AFCAPS/TexCAPS which showed that in over 6000 people without coronary disease and with average cholesterol levels (chol 4·65–6·82 mmol·l⁻¹; LDL-C 3·36–4·91 mmol·l⁻¹), reduction in LDL cholesterol by 25% using lovastatin led, over 5 years follow-up, to a 37% reduction in acute cardiac events[5]. So patients with coronary disease, and those at even moderate risk of future development of such disease benefit significantly from statin therapy. Now it is also looking as if there is a significant reduction in non-haemorrhagic stroke with long-term statin treatment in patients with coronary disease[6]. Combining the 13 000 patients from CARE and LIPID, there was a 22% reduction in total strokes, and a 25% reduction in non-fatal strokes.

In this edition, Wilhelmsen and his colleagues from the 4S study group[7] have, using their excellent database, looked at the risk factors that play a part in subsequent major coronary events in those with prior myocardial infarction, and assessed the impact of predicted risk on the benefit of cholesterol-lowering treatment. The majority of patients in the 4S study had been included in the stable phase following myocardial infarction, and thus, the present report, analysing 3525 patients, would not be expected to come up with very different prognostic findings from the cholesterol reduction viewpoint, as it includes approximately 78% of the original cohort. With regard to risk factors, those with a longer period between myocardial infarction and subsequent randomization to 4S had the highest subsequent end-point incidence, and subsequent events were more common in those with more than one infarction prior to inclusion, in those with hypertension, in those who continued to smoke following their index myocardial infarction, and in diabetics. Presumably many of these risk factors were in play prior to the time of the index infarction which made these patients suitable for the 4S trial in the first place, and thus it is not surprising that they continue to be so following such an index event. The authors found that, while there was no difference in the relative benefit from simvastatin in those post-infarction patients at low, medium, and high risk, the absolute benefit of simvastatin treatment doubled from the lowest to the highest tertile of risk.

This latter finding reflects a likely important interplay between cholesterol and other recognized risk factors such as smoking, hypertension, and diabetes, and may help us when considering who to treat particularly amongst ‘normal’ populations. It is likely that treatment benefit will be greater in those with an elevated cholesterol/LDL-C in association with other
risk factors[8], and thus the often difficult decision to institute cholesterol lowering therapy as primary prevention should be eased by the presence of other risk factors, which of course will need simultaneous and appropriate modification. Many of these subjects do not want to ‘take tablets for the rest of their lives’; and, while this is quite understandable, it is essential that the medical profession emphasizes to such subjects the importance of an atherogenic lipid profile, particularly in conjunction with other risk factors. It must be explained that all such risk factors can be very effectively treated, and, most important, that ‘the rest of one’s life’ may be considerably shorter than necessary if an atherogenic lipid profile is ignored. To date we have been relatively unsuccessful in this regard, either not wanting to burden the person with medications and a ‘disease’ label, or the person not wanting to take tablets. Whatever the reason, premature coronary disease remains the biggest killer in the western world, and it seems a perfect opportunity, with all the positive findings from the various trials to ‘seize the moment’ and adopt an aggressive therapeutic approach, even in at-risk subjects.

From the secondary prevention viewpoint the 4S study (and many of the other major studies) may never be possible to repeat if we are doing our job properly and acting on the basis of their findings. The majority of patients included in the 4S trial had suffered at least one myocardial infarction at least 6 months prior to enrolment, and the cholesterol level for inclusion had to be between 5·5–8·0 mmol·l⁻¹ at enrolment, so it is likely that many patients had little attempted intervention on their lipid profile after presentation with their acute index event, and before inclusion in the trial. It is surely time for us to commence aggressive lipid lowering treatment in the coronary care unit setting on the basis of their knowledge that we have. This will ensure that all patients presenting with acute coronary syndromes will have immediate attention to their risk profile. Recent studies have shown no significant safety problems from introduction of statins in the acute phase. ‘If we assume, to a greater or lesser extent, a patient’s cholesterol/LDL-C is too high if they have an acute cardiac event, then the aggressive approach to cholesterol reduction appears a reasonable one’[9]. The old age habit of waiting for weeks to perform fasting lipids, then to review at outpatients to consider the results is fraught with difficulties. These include: the test never being done, or the consigning of a very abnormal profile unnoticed to the back of the chart. It is also likely that compliance with medications commenced in the acute setting will be significantly better adhered to in the long-term than if medications are commenced weeks or months after the patient has recovered and feels well (and doesn’t want to take medications for the rest of their lives).

So, exciting times in the cholesterol game. There are significance reductions in cardiac events over the long-term with statin treatment, reductions which would make any cardiothoracic surgeon or angioplastier proud. Benefit from treatment in terms of stroke reduction is looking good[6]. Long-term safety profile is looking good to date, including when treatment is started in the acute phase. Wilhelmsen and his colleagues remind us again of the importance of the classic risk factors, and of the benefits of statin treatment post-myocardial infarction[7]. Surely it is now time to view cholesterol/LDL-C reduction as a major therapeutic intervention, and to act accordingly? I commence treatment on all patients in the CCU setting who have an LDL cholesterol >3·0 mmol·l⁻¹. Further studies will confirm if this is indeed the way to go.

D. MULCAHY
Tallaght Hospital,
Dublin, Ireland

References