How one of medicine's best-conducted major clinical trials transformed cardiovascular care for people with diabetes

John Betteridge

In 1994 there was a special closed meeting in Dallas to discuss the results of what turned out to be one of the best-designed and best-conducted major clinical trials that has ever been carried out in any area of medicine. When presented the following day at the late-breaking session of the *American Heart Association Scientific Sessions* by Professor Terje Pedersen and his colleagues, the excitement among the thousands of delegates was palpable. Here was a simple treatment that any physician could prescribe which was safe and could significantly reduce the risk of overall mortality and major coronary events in people with established heart disease. The study was the Scandinavian Simvastatin Survival Study, known by every one as '4S' (4S Group, 1994). It is important to put this study into perspective and to show how it transformed medicine for many sub-groups, including people with diabetes.

In the 1980s and early 1990s there was tremendous controversy, not so much about the relationship between cholesterol and atherosclerosis (although some powerful figures in cardiology dismissed it) but about the effects of treatment. Early trials had provided inconclusive results, with regard to the benefits of lipid lowering, for a variety of reasons. Clinical trial science was in its infancy; the need to accrue enough end points with as near complete follow-up as possible was not always appreciated. In addition the available drugs were relatively ineffective, poorly tolerated or both. This led to there being little difference in mean cholesterol between the treated and placebo groups (Betteridge and Morrell, 2003).

Nevertheless these early trials did show a reduction in coronary events, particularly non-fatal myocardial infarction. Overall mortality was unaffected, although the trials were not powered to detect changes in this parameter. Probably by chance, small increases were seen in some of the studies in non-coronary mortality, such as suicide, violent death and cancers of the gastrointestinal tract. This led one distinguished professor of medicine to remark that the only effect of lipid lowering was to change the diagnosis on the grave stone: the person did not die of a broken heart but suicide, violent death or cancer.

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At the height of the so-called 'cholesterol controversy', a particularly striking headline appeared in *The Guardian* on St Valentine's Day 1992; it pronounced 'Murders linked to low fat drugs'. Some of my patients arrived in clinic clutching this cutting complaining that I was potentially turning them into murderers! In fact there were two murders in the early trials, one in the Helsinki Heart Study and one in the Lipid Research Clinics Coronary Primary Prevention Trial. However, these two individuals were not vicious murderers; they were murdered! It is difficult to conceive of a biological reason as to how taking a lipid-lowering agent would make you more likely to be murdered. I remember learned articles and editorials in *The Lancet* (Morgan et al, 1993) and other journals (e.g. Ryman, 1994) discussing the potential biological link between cholesterol lowering, suicide and violent death.

It was the introduction of the statins that enabled definitive clinical trials to be performed, as they were highly effective and well tolerated, leading to substantial differences between the treated and the placebo groups. Furthermore clinical trial science had come on a pace and the importance of statistical power had begun to be appreciated. The statins were discovered in the 1970s, more or less simultaneously, in Japan by Endo and in the USA by Alberts (Betteridge and Morrell, 2003). They were isolated from culture broths of penicillin. They proved to be specific, competitive inhibitors of the rate-determining enzyme in cholesterol synthesis, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase. By reducing hepatic cholesterol synthesis, low-density lipoprotein (LDL)-cholesterol receptors are up-regulated and are able to take up more plasma LDL-cholesterol, with a consequent reduction in plasma levels.

4S used simvastatin at a dose of 20–40 mg/day in people with hypercholesterolaemia and a history of symptomatic coronary heart disease (CHD). To have the statistical power to answer the question on overall mortality it was necessary to continue the trial until 440 deaths had occurred. The study was remarkable in its execution, and complete follow-up of the 4444 participants was obtained. Professor Pedersen tells amazing stories of how he personally tracked down participants who had previously been lost to follow-up. 4S is often used in the teaching of clinical pharmacology as the paradigm of the randomised controlled trial (RCT).

The cause of the excitement in Dallas was the finding from 4S of an impressive 30% reduction in overall mortality with the statin treatment. It is not often that such landmark trials come along and I am often asked

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why the results of 4S took so long to be incorporated into routine clinical practice. It was to a large extent, in my view, due to the previous controversy, which meant that some physicians were reluctant to accept the 4S results.

As further statin trials were published for both primary and secondary prevention (Betteridge and Khan, 2004), the evidence for cholesterol lowering developed into one of the largest data sets of RCTs on which to base clinical decisions. It became clear that people with diabetes and symptomatic CHD showed the same benefit for the reduction of major coronary events as people without diabetes.

More recent trials – such as Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22; Cannon et al, 2004), Treating to New Targets (TNT; LaRosa et al, 2005) and Incremental Decrease in End Points through Aggressive Lipid Lowering (IDEAL; Pedersen et al, 2005) – point to the greater benefits of more intensive LDL-cholesterol lowering, with further reduction in the residual risk of subsequent events. This has led the American Heart Association (AHA; 2004) to propose a more intensive goal of therapy for LDL-cholesterol (<1.8 mmol/l) for those at highest risk, including people with diabetes and established CHD.

People with diabetes are more likely to die with their first vascular event. This emphasises the importance of primary prevention. Important information has come from the Heart Protection Study (HPS; HPS Collaborative Group, 2002) with simvastatin and the Collaborative Atorvastatin Diabetes Study (Colhoun et al, 2004). Importantly the benefits of LDL-cholesterol lowering were observed regardless of the baseline LDL-cholesterol or indeed other lipid parameters. These findings have changed the approach to treatment, moving from the concept of treating hyperlipidaemia to the treatment of high cardiovascular disease risk. As a result statins are now recommended in high-risk individuals, including those with diabetes, irrespective of baseline LDL-cholesterol levels.

A major bonus of statin therapy was the reduction in stroke, which is consistent across the trials. This would not have been predicted by most of the epidemiology studies. It is still disappointing to discover in clinical audits that many people do not receive appropriate statin therapy, and continued efforts are required in physician education.

The future looks exciting with the development of new therapeutic agents targeting important components of diabetic dyslipidaemia, particularly low high-density lipoprotein-cholesterol. These developments may turn out to be just as exciting the development of statins.

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