Statins for people with diabetes

See Articles page 117

Statins are among the most notable triumphs of modern medicine. Since the demonstration of reduction in mortality in the Scandinavian Simvastatin Survival Study (4S) study in 1994,[1] these lipid-lowering drugs have become widely used in people with or without known cardiovascular disease and in people with average as well as high cholesterol concentrations. In recent years, generic formulations have made the drugs affordable for more people.

7% of people in the USA have diabetes mellitus,[2] and the prevalence is higher in Asia.[3] Patients with diabetes have increased susceptibility to cardiovascular disease. Indeed, the coronary risk of a person with diabetes is similar to that of a person without diabetes who has had a previous myocardial infarction. Guidelines recognise the increased cardiovascular risk in patients with diabetes and endorse the use of statins in people with diabetes at risk of cardiovascular disease.[4]

Despite the widespread use of statins in patients with diabetes, there are some unanswered questions. For example, do statins confer more or less benefit to patients with diabetes than to people without the disorder? Would glycaemic and blood-pressure control affect the benefit of statins? Are statins beneficial in those with hypertriglyceridaemia, low HDL, or both?

Just when the benefits of statins seemed to be beyond reasonable doubt, two randomised studies found no clear benefit of statins in patients who had diabetes: the German Diabetes and Dialysis Study (4D)[5] and the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN).[6] In 4D, 1255 patients with diabetes on dialysis were assigned to atorvastatin or placebo for about 4 years. There was an 8% reduction in the primary endpoint of myocardial infarction, cardiac death, or stroke that was not statistically significant. In ASPEN, there was a 10% reduction (again, not statistically significant) in the primary endpoint. Very recently, the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) reported an 8% reduction in the primary endpoint (not statistically significant), despite 45% lower LDL concentrations in those treated with rosuvastatin 10 mg daily.[7] In this trial, 30% of the participants had diabetes.

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The meta-analysis in today's *Lancet* by the Cholesterol Treatment Trialists Collaborators[8] therefore explores a very important issue: whether statins are as beneficial in patients with diabetes as in those without diabetes with respect to different outcomes, and whether the benefits depend on the type of diabetes, lipid profile, or other factors. The meta-analysis benefited from data on very large numbers of individual trial participants, which enabled detailed and prespecified subgroup analysis. The findings are reassuring: there was a 9% proportional reduction in all-cause mortality per mmol/L reduction in LDL cholesterol in participants with diabetes (rate ratio [RR] 0·91, 99% CI 0·82–1·01), which was similar to the 13% reduction in those without diabetes (0·87, 0·82–0·92). There were significant reductions in the numbers of fatal and non-fatal myocardial infarctions, coronary revascularisations, and strokes. Moreover, the relative-risk reduction was similar irrespective of previous history of vascular disease and baseline characteristics.

However, the meta-analysis did not include the recent negative trials—4D, ASPEN, and CORONA—nor did it include small trials, unpublished trials, or trials published in languages other than English. Nevertheless, the addition of 4D and ASPEN did not affect the estimated rate ratios. Although there were no significant reductions in the composite primary endpoints in 4D, ASPEN, and CORONA, the reductions in fatal and non-fatal myocardial infarction were 15%, 26%, and 17%, respectively. These reductions

were not individually statistically significant, but were clearly consistent with the findings of the meta-analysis. Importantly, there was no question of harm. Thus there is no need to change current practice for statins in patients with diabetes. In the near future, trials such as the Study of Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) and Study of Heart and Renal Protection (SHARP) will be completed and shed further light on this issue.

While statins are expected to reduce the incidence of fatal and non-fatal myocardial infarctions, they are not a panacea, and patients on statins are liable to other causes of morbidity and mortality. In any case, treatment decisions should be based not on the reduction in relative risk but on the reduction in absolute risk or its reciprocal, the number needed to treat.[9] If a patient has a high absolute cardiovascular risk, even a modest reduction in relative risk gives meaningful clinical benefits. Additionally, one should consider life expectancy, concomitant diseases, and quality of life.[10] Apart from drug treatment, one must not forget the importance of lifestyle changes, such as cessation of smoking, healthy diet, and regular exercise.

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Sedation in the intensive-care unit: good and bad?

See **Articles** page 126

During mechanical ventilation, sedation and analgesia are given to reduce discomfort and pain, and to minimise oxygen consumption, all of which are extremely important for critically ill patients. Risks exist for both undersedation and oversedation. Oversedation is probably very frequent in today's intensive-care units,[1] and a trial by Kress and colleagues of spontaneous awakening (ie, daily interruption of continuous intravenous sedation in mechanically ventilated patients) has been shown to substantially reduce the time on ventilation.[1] The benefit for patients is twofold. First, sedative drugs accumulate in the body far beyond the treatment period. Second, a lack of awakening led clinicians to expose patients to unnecessary neurological imaging.[1]

In today's *Lancet*, Timothy Girard and co-workers[2] present a multicentre randomised trial in which they assessed a wake up and breathe protocol in 336 mechanically ventilated patients. These investigators wanted to extend the Kress protocol and to combine daily spontaneous awakening trials with subsequent spontaneous breathing trials involving ventilator weaning in a two step approach. The Girard protocol resulted in more days breathing without assistance (3·1 additional days in the 28-day study, 95% CI 0·7–5·6), earlier discharge from both intensive-care units and hospitals, and better 1-year survival than patients in the control group, who received patient-targeted sedation plus a daily spontaneous breathing trial. At first sight, these results seem to reinforce the idea that accumulation of sedation can be avoided or minimised with benefit for patients. But sedation is also an important component of care for critically ill patients, and before we adopt Girard's approach, critical appraisal of their study and of the care delivered in the control group is needed.

One surprising aspect of Girard and colleagues' control group was that there was no requirement for sedatives