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**Now is good, earlier is better**

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There is abundant evidence that lowering LDL cholesterol with statins reduces cardiovascular risk both in those without symptomatic atherosclerotic disease (primary prevention), and those who have already suffered an atherosclerotic complication, such as a myocardial infarction or ischaemic stroke (secondary prevention).<sup>1</sup>

Few clinicians would argue against the use of statins in secondary prevention, and high risk primary prevention, for example patients with familial hypercholesterolaemia. However, there is considerable resistance to using statins in moderate risk primary prevention patients, on the basis that the benefit may not outweigh the risk.<sup>2</sup> One of the issues in this debate is the limited data on the magnitude of the CV risk reduction obtainable by lowering LDL cholesterol for decades, as opposed to the few years to which practical considerations limit a randomised clinical trial. Packard and his Glasgow collaborators now provide new information about the benefit of lower plasma concentrations of LDL cholesterol over long periods of time.<sup>3</sup>

The West of Scotland Coronary Prevention Study (WOSCOPS)<sup>4</sup> was the first randomised controlled trial (RCT) to test the effectiveness of lipid-lowering with a statin in a primary prevention population: 6595 men without a history of myocardial infarction were randomised to pravastatin 40 mg or placebo, and followed for 4.9 years. Pravastatin decreased the primary outcome measure, nonfatal myocardial infarction plus coronary heart disease (CHD) death, by 31 percent (95% CI 17-43%,  $p < 0.001$ ), and substantial cardiovascular benefit was still evident 15 years after the end of the randomised comparison.<sup>5</sup> Using data from prolonged follow-up of the WOSCOPS participants, not only those randomised but also about 75,000 male patients aged 45-64 who were screened (including a total cholesterol measurement) but not randomised, the Glasgow group extend

their series of WOSCOPS follow-up papers.<sup>6</sup> Screening and randomisation took place in 1989-1991, and the observations presented in the current paper have a cut-off date of 2011, thus covering two decades, at the end of which the average age of the participants was 75. This represents a reasonable estimate of the risk of premature major coronary events including cardiovascular death over a considerable proportion of later life. National electronic hospital discharge records and mortality registries provided information on clinical events and duration of hospitalisations. The investigators modelled the effect of higher total cholesterol values on CHD events and hospitalisations, validating their models by using the reduction in major coronary events resulting from lowering blood cholesterol during the randomised trial.

No epidemiological study can match the rigour of a double-blind RCT, and the authors acknowledge possible confounding factors. Nevertheless, large cardiovascular outcome trials require massive international organisation and are enormously costly (typically several hundred million dollars), and are difficult to keep going for more than about 5 years of follow-up. Therefore, estimation of the benefits of lipid-lowering treatment in adulthood over decades can only be obtained via extrapolation beyond the active follow-up period of RCTs, which requires various assumptions, or by gathering whatever data are available on former study participants and using epidemiological modelling methods, as was done here. The standard methods of survival analysis typically used in cardiovascular RCTs are based on time to the first event, so second and subsequent events are not included in the main analysis. However, the second myocardial infarction may be just as devastating as the first and is just as important for health economic analyses, and so the methods used by the Glasgow group counted all relevant events occurring during the 20-year observation period.

The modelled benefit of having lower cholesterol levels were substantial in patients with and without CHD at baseline. Over 20 years, lowering total cholesterol by 1 mmol/L in men with average cholesterol and without clinically apparent CHD was estimated to prevent about 9 coronary events and 56 days in the hospital per 100 patients. In those who already had CHD at screening, the corresponding numbers were about 30 events and 200 hospital days. These observations are entirely consistent with the findings of RCTs, which have consistently shown that statins reduce cardiovascular risk in a broad array of patient types, and to date have not found any threshold below which lowering LDL cholesterol by any method is futile or unsafe.<sup>1 7 8</sup>

The model also found that lowering blood cholesterol starting early in middle age (age 45-54) is likely to be more effective for preventing CHD events than doing so later (age 55-64). This is consistent with the generally accepted view that atherosclerosis begins with fatty streaks in the arterial endothelium, which are not infrequently found in young healthy individuals, especially men in their 30s or even 20s. Although diet and lifestyle changes can produce small reductions in LDL cholesterol, pharmacotherapy, which will almost always include a statin, is required for a substantial effect. Early treatment to prevent the complications of atherosclerosis, such as myocardial infarction, is vigorously advocated by some,<sup>9</sup> but is controversial. Treatment cost is generally not an important consideration: six of the 7 marketed statins are available in generic form, with competition between multiple manufacturers keeping the price low. However, some fear that the strategy over-medicalises large numbers of healthy people.

In recent years a perception has developed that many patients cannot tolerate statins because of various subjective non-serious adverse events attributed to the statin,

particularly muscle symptoms without significantly elevated creatine kinase. In double-blind RCTs, however, there is very little difference in the incidence of these adverse events between statin and placebo, indicating that they are predominantly non-pharmacological; rather, they are largely driven by patient expectations (the nocebo effect).<sup>10 11 12</sup> These are fuelled not only by necessary clinician advice to report unexplained muscle symptoms (so that CK can be checked to diagnose, or much more commonly rule out, myopathy), but also and more importantly, widespread misrepresentation of statin adverse effects.<sup>10, 13, 14</sup>

Overall, not only is the risk of statin treatment often exaggerated, but the benefits may be underestimated, because they are based on the results of trials lasting only a few years,<sup>15</sup> while the underlying disease progresses slowly over decades. So, with no strong economic deterrent to statin therapy and given findings from genetic studies which show substantial cardiovascular benefit in the context of modest but lifelong differences in LDL cholesterol, should we not consider lifetime risk, as opposed to 10-year risk, and start treatment earlier when indicated? Age is the dominant risk factor in 10-year risk scores with the result that younger individuals at substantially higher risk than their peers may not qualify for risk-lowering treatment because their absolute risk remains below the selected threshold. By contrast, simply by ageing all older adults eventually qualify for the same treatment, even if they have no notably abnormal modifiable risk factors. This results in treatment for the high risk younger patient being postponed unnecessarily – an opportunity missed. Some countries have taken tentative steps towards the concept of lifetime risk. For example, age differentiated risk thresholds have been implemented in Norway<sup>16</sup> and are being considered elsewhere. Lifetime risk or age differentiated approaches to the allocation of risk-lowering treatment will require a shift in how clinicians consider risk. The Glasgow

group's estimates of the real long-term burden of CHD provide valuable information to support such a shift.

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