

## Statins and micronutrients: unanswered questions

In an accompanying paper (p. 461),<sup>1</sup> Dr Thompson and Dr Temple offer several objections to the evidence underlying the widespread and growing use of statins. First, in the trials of effectiveness, statins were not compared with dietary management, which is the most appropriate alternative intervention. Second, the varying endpoints of such trials give the impression of having been chosen to yield favourable desired outcomes. Third, the evidence is presented in a way that exaggerates their apparent effectiveness (in terms of relative rather than absolute risk). They argue that, as statins are given to ever greater numbers of low-risk individuals, the economic case for their use diminishes. This provocative critique will doubtless generate debate but it begs a further question: who should be targeted for statin therapy? Paradoxically, as evidence of the effectiveness of these drugs has accumulated, this question has become more difficult to answer.

Statins were identified as putative agents to prevent cardiovascular disease because of their direct effect on the enzyme HMG-CoA reductase, a critical step on the pathway of cholesterol synthesis. Consequently, initial studies focused on their ability to reduce cholesterol and by this means decrease the risk of cardiovascular events. Yet there is now considerable evidence that additional mechanisms are involved in their beneficial effects. This became clear even in the earliest studies, with the West of Scotland Coronary Prevention Study finding that the reduction in cardiovascular events emerged at about six months after initiation of therapy, somewhat faster than would be predicted by cholesterol reduction alone.<sup>1</sup> Subsequent trials that have not been limited to individuals with high lipid concentrations indicate that the benefits are largely independent of initial low-density lipoprotein (LDL) and total cholesterol concentrations.<sup>2</sup> When we look at the results of non-statin cholesterol-lowering agents we see that statins reduce the risk of myocardial infarction more than would be predicted from the reduction in cholesterol achieved.<sup>3</sup> Yet statins continue to be regarded primarily as lipid-lowering drugs—not only in practice, with recommendations for prescription, but also in the preference given, when new statins are selected, to those taken up predominantly by the liver, where cholesterol synthesis takes place.

With the recognition that statins have other mechanisms of action, attention has switched particularly to vascular endothelium. The integrity and function of the endothelium depends on various mechanisms involving synthesis of nitric oxide (NO), including vascular relaxation and inhibition of smooth muscle proliferation, endothelial leukocyte adhesion, and platelet aggregation. Oxidized LDL exerts some of its atherogenic effects by inhibiting the generation of NO by nitric oxide synthase. Thus, the reduction in LDL brought about by statins will by itself increase concentrations of NO and enhance endothelial function.<sup>4</sup> However, statins also act directly to increase activity of nitric oxide synthase, working through a separate mechanism that is not inhibited by LDL.<sup>5</sup> This provides at least one plausible explanation for the lipid-independent effects of statins—and one that is supported by a growing volume of experimental evidence.<sup>6–9</sup> However it does not help in deciding who might benefit from receiving them.

Matters are complicated further when we see that nitric oxide synthase activity, and thus endothelial function, is influenced by a range of other factors, including some common dietary components acting on the metabolism of homocysteine, an amino acid produced from methionine in dietary protein. Homocysteine is metabolized either by a reversible process of methylation, which requires folic acid and vitamin B<sub>12</sub>, or by irreversible breakdown of cysteine, which involves vitamin B<sub>6</sub>.<sup>7</sup> An increased concentration of plasma homocysteine is associated with an excess risk of cardiovascular disease.<sup>8,9</sup> However, 5-methyltetrahydrofolate, the main circulating metabolite of folic acid, increases NO production in addition to any effects mediated via reduction of homocysteine. Supplementation with high-dose folic acid (5 mg daily) has now been shown to enhance endothelial function.<sup>9</sup> Thus, both statins and several common micronutrients influence endothelial function by their action on cellular nitric oxide. The antiatherogenic effects of other dietary components may be achieved via different mechanisms. For instance, glitazones, a component of certain vegetables, might protect damaged endothelium by inhibiting leucocyte adhesion.<sup>10</sup>

A further layer of complexity emerges from work on diabetes. The Heart Protection Study, which looked explicitly at the effect of simvastatin on outcomes in diabetes, reported a reduction in risk of vascular events of about a quarter, irrespective of initial LDL cholesterol concentrations;<sup>11</sup> yet studies in which patients with type 2 diabetes had several weeks of intensive LDL-lowering with

atorvastatin<sup>12</sup> or simvastatin<sup>13</sup> showed no effect on NO-dependent vascular reactivity—unlike folic acid, which did restore NO-dependent vasodilatation.<sup>14</sup> A longer study of atorvastatin (six months) in patients with type 2 diabetes did reveal improvements in vascular reactivity independent of the LDL reduction achieved.<sup>15</sup> These improvements were noted to correlate with reductions in C-reactive protein—an observation that led to the suggestion that, in these patients, the endothelial benefits of statins might be attributable to their anti-inflammatory properties. Finally, another study has shown that, in individuals with type 1 diabetes but not in healthy controls, administration of vitamin C enhances endothelium-dependent vasodilatation.<sup>16</sup> Vitamin C reverses endothelial dysfunction by enhancing NO production: it stabilizes and increases intracellular concentrations of the essential endothelial cell NO-synthase cofactor tetrahydrobiopterin.<sup>17</sup>

These findings, together with other evidence such as that from the Lyon Heart Study,<sup>18</sup> which showed that dietary modification can yield benefits considerably greater than those reported with statins, indicate a need for a much better understanding of the mechanisms by which statins and micronutrients, individually and in combination, act to reduce atherogenesis. For some researchers, this will require a new way of thinking. Thus, a recent trial found that folic acid conferred no additional benefit in patients taking statin therapy, despite some evidence of a beneficial effect on its own.<sup>19</sup> An alternative interpretation, seemingly not considered, is that statins may confer little additional benefit in people taking folic acid.

Some of these issues are being addressed in trials underway that are looking at the effectiveness of statins and folate, combined and individually—for example, the SEARCH (Study for Evaluation of Additional Reductions in Cholesterol and Homocysteine) [www.ctsu.ox.ac.uk]. However, the main message is that, if we are to make the best of what common micronutrients and statins can offer against vascular disease, we need to know much more about their mechanisms of action.

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