

# ANALYSIS

## Should people at low risk of cardiovascular disease take a statin?

A review of statins for primary prevention of cardiovascular disease could alter guidance for those with a 10 year risk of less than 10%. **John Abramson and colleagues** argue that statins have no overall health benefit in this population and that prescribing guidelines should not be broadened

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The 2013 Cochrane review of primary prevention with statins concluded that they reduce all cause mortality and cardiovascular events without increasing the risk of adverse events among people at low risk of cardiovascular disease (<10% over 10 years).<sup>1</sup> However, just two years earlier, a Cochrane review had concluded that existing evidence did not support the use of cholesterol lowering statins for people with <20% 10 year cardiovascular risk: “Only limited evidence showed that primary prevention with statins may be cost effective and improve patient quality of life. Caution should be taken in prescribing statins for primary prevention among people at low cardiovascular risk.”<sup>2</sup> This conclusion was consistent with the 2006-08 guidance from the National Institute for Health and Care Excellence (NICE)<sup>3</sup> and the 2011 update of the American Heart Association’s guidelines for the prevention of cardiovascular disease in women, both of which recommended statin therapy only when the 10 year risk of disease is 20% or greater.<sup>4</sup>

If risk is estimated using the QRISK2 score,<sup>5</sup> by the 2011 standards just 2% of women in their 50s and 16% in their 60s qualify for statin therapy ( $\geq 20\%$  10 year risk of cardiovascular disease). For men, 9% in their 50s and 48% in their 60s qualify.<sup>6</sup> Under the proposed 2013 standards, however, no level of risk would preclude statin therapy, raising the question whether all people over the age of 50 should be treated.<sup>1 7</sup> We argue that the evidence does not show that the benefits of statins in low risk patients outweigh the harms and that the advice for treatment of this group should not be changed.

### Why did Cochrane change its advice?

Although the results of four additional clinical trials were included in the 2013 review, these did not substantially alter the previously documented effect of statin therapy. Instead, the change in advice was based on a meta-analysis by the

Cholesterol Treatment Trialists’ (CTT) Collaboration published in 2012. The collaboration was established to conduct meta-analyses of patient level data from all relevant clinical trials of statins to investigate non-aggregated outcomes (such as myocardial infarction) and effects on subgroups that single studies were inadequately powered to evaluate.<sup>8</sup>

The 2012 meta-analysis was designed to assess the “overall net benefit” of cholesterol lowering with statins in the subgroup of participants at low risk of cardiovascular disease, defined as five year risk <10%,<sup>9</sup> in 27 clinical trials that had been published by the end of 2009.<sup>10</sup> The average five year risk in participants in this group was 2.6%. The authors concluded that statin therapy significantly reduces the risk of all cause mortality by 9.1% and of major vascular events—including major coronary events (non-fatal myocardial infarction or coronary death), strokes, and coronary revascularisation procedures—by about 20% per 1.0 mmol/L reduction in low density lipoprotein (LDL) cholesterol regardless of baseline risk level. The authors calculated that in low risk patients, statins prevented 11 major vascular events per 1000 people treated for five years for each 1.0 mmol/L reduction in LDL cholesterol. They concluded that this significant benefit of statins in low risk patients “greatly [exceeded] any known hazards of statin therapy.”

### Examining the data

Although these figures sound good, closer examination raises questions about both the benefits and harms. The endpoint that is most encompassing, and least subject to bias, in statin trials is all cause mortality.<sup>5</sup> It is rarely misdiagnosed and not susceptible to inaccurate determination of cause. We used data from figure 3 of the CTT meta-analysis to calculate all cause mortality in low risk patients (< 5% and 5 to <10% over five

years). Our calculations (table 4) show that statins do not have a significant effect on overall mortality in this group of patients (relative risk=0.95, 95% confidence interval 0.86 to 1.04).

After all cause mortality, “hard” cardiovascular endpoints—cardiovascular death, myocardial infarction, and stroke—are the most reliable because they minimise subjective input and are least vulnerable to bias in adjudication.<sup>9</sup> These hard endpoints are also most important because they permanently affect people’s lives. Some studies, including CTT publications, have increased statistical power by including “softer” outcomes such as coronary revascularisation procedures. However, rates of revascularisation are less precise because of geographical variations in thresholds for intervention and because treatment allocation is largely unblinded, made apparent by the lower total and LDL cholesterol levels in people assigned to the statin arms of the clinical trials. Bias resulting from unblinding has been documented for all outcomes except all cause mortality, particularly subjectively determined outcomes.<sup>11</sup>

In the CTT meta-analysis 35% of the “major vascular events” that occurred in people with a five year risk of <10% were coronary revascularisation procedures. Conversely, 65% of major vascular events were “hard” events (major coronary events and stroke), and thus the reduction in hard cardiovascular events in patients at low risk treated with statins was 7.15 (0.65×11) per 1000 low risk patients treated for five years. In other words, 140 low risk people must be treated with statins for five years to prevent one major coronary event or stroke, without any reduction in all-cause mortality. The five year absolute reduction in myocardial infarction and stroke for the lowest risk patients (< 5% risk over the next five years) was 0.6%. This means that 167 such people needed to be treated with a statin for five years to prevent one hard cardiovascular event.

The best indication of the net effect of a treatment on overall health is the total number of serious adverse events—which include deaths from all causes, hospital admissions, prolongations of admission, cancer, or permanent disability. Despite having access to patient level data, the CTT meta-analysis did not consider the effect of statins on serious adverse events. Only three of the five largest trials included in the meta-analysis (JUPITER, ASCOT, and LIPID) reported data on serious adverse events, none of which found a reduction associated with statins.

The 2013 Cochrane review relied on two earlier reviews that included only published data to conclude the rate of serious adverse events was similar in the statin and placebo groups. Cost effectiveness analysis based on reduction in cardiovascular events without consideration of overall rates of serious adverse events is meaningless—all events are costly. Moreover, with no reduction in all-cause mortality and no evidence of reduction in total serious adverse events for patients with five year cardiovascular risk of <10%, the net benefit-harm equation has zero overall benefit (the small reduction in serious cardiovascular events is counter-balanced by a non-specified increase in other serious adverse events) and ignores the clear evidence of harm that has been demonstrated in clinical trials and observational studies. A retrospective cohort study found that 18% of statin treated patients had discontinued therapy (at least temporarily) because of statin related adverse events. Forty per cent of the adverse events were related to musculoskeletal symptoms.<sup>12</sup>

## Known harms

### Myopathy

The excess risk of myopathy associated with statins reported in the CTT meta-analysis is 0.5 per 1000 patients over five years—number needed to harm (NNH) is 2000. However, a cross sectional analysis from the National Health and Nutrition Examination Survey database shows that the prevalence of muscle pain in statin users is 50% greater than in non-users. In absolute terms, this increase in muscle pain is 100 times greater than that reported in clinical trials—53/1000 patients, NNH=19.<sup>13</sup> A retrospective cohort study that included 13 626 people taking statins and 32 623 controls found a greater incidence of musculoskeletal disorders overall and injuries in those taking statins (odds ratio 1.19, 95% confidence interval 1.08 to 1.3 and 1.13, 1.05 to 1.21, respectively). The NNH for musculoskeletal disorders and injuries in people taking statins were 47 and 37, respectively.<sup>14</sup>

A randomised controlled trial found that improvement in cardiorespiratory fitness over 12 weeks of exercise training was significantly attenuated in 18 overweight or obese participants treated with simvastatin 40 mg compared with the fitness in 19 treated with placebo, 1.5% and 10% improvement, respectively,  $P<0.005$ .<sup>15</sup>

### Diabetes

CTT authors reported a 10% increase in the relative risk of developing diabetes while taking statins, yielding an estimated excess of five new diagnoses per 1000 people treated with a statin for five years. However, data from the JUPITER trial show a 25% increase in frequency of physician reported incidence of diabetes associated with statin therapy overall and a 50% increase in women, corresponding to an estimated 11 new diagnoses per 1000 women taking statins over 1.9 years<sup>16</sup>—more than five times the frequency reported by CTT. Possible explanations of the increased frequency of diabetes associated with statin therapy in the JUPITER study include increased frequency of diabetes risk factors in the study population, increased risk associated with drug potency, or increased ascertainment of new onset diabetes. Even in the JUPITER study, new diagnoses of diabetes were based on physician report rather than study related monitoring, which suggests the possibility of under-ascertainment of new cases of diabetes within clinical trials. Observational data from the Women’s Health Initiative trial show a 48% increase in the risk of new onset diabetes associated with statins in post-menopausal women.<sup>17</sup>

### Others

Statin therapy has been associated with a wide range of adverse events including liver dysfunction, acute renal failure, and cataracts;<sup>18</sup> cognitive symptoms, neuropathy, and sexual dysfunction;<sup>19</sup> decreased energy and exertional fatigue;<sup>20</sup> and psychiatric symptoms, including depression, memory loss, confusion, and aggressive reactions.<sup>21</sup> On the positive side, statins have been associated with a decreased risk of oesophageal cancer.<sup>18</sup>

## Limitations of research data

All of the randomised controlled trials included in the CTT meta-analysis were funded by the manufacturer of the statin being studied. A recent Cochrane review found that industry sponsored clinical trials are significantly more likely than

non-commercially funded studies to report favourable efficacy and safety results and conclusions.<sup>22</sup>

Possible mechanisms by which adverse effects might be minimised in clinical trials include exclusion of up to 30% of patients with comorbidities (such as liver, kidney, muscle or inflammatory diseases), prerandomisation run-in periods in which people who fail to tolerate statins are excluded, 10% dropout rates, failure to assess for specific potential adverse events (like myopathy or cognitive changes), and underascertainment and selective reporting of adverse events (including serious adverse events).<sup>23</sup>

The Cochrane authors acknowledge that reporting of adverse events in these trials is generally poor, “with failure to provide details of severity and type of adverse events or to report on health-related quality of life.”<sup>21</sup> Nevertheless, the 2013 review concluded that even in the absence of high quality evidence it is “unlikely” that any “major life-threatening hazards associated with statin use exist.” However, the large discrepancies between the frequency of adverse events reported in commercially funded randomised controlled trials included in CTT meta-analyses and non-commercially funded studies show that determination of harms cannot be left to industry alone.

Additionally, the benefit of statins found in clinical trials may be exaggerated because prerandomisation screening procedures include monitoring for compliance with therapy, which led to adherence rates in five of the landmark clinical trials included in the CTT meta-analysis of 70-94%.<sup>24</sup> In community based studies of drug use, at least 50% of patients discontinue statin therapy within one year, and adherence to statin therapy for primary prevention in people over 65 was only 25% after two years.<sup>25</sup>

## The bottom line

Our calculations using data presented in the 2012 CTT patient level meta-analysis show that statin therapy prevents one serious cardiovascular event per 140 low risk people (five year risk <10%) treated for five years. Statin therapy in low risk people does not reduce all cause mortality or serious illness and has about an 18% risk of causing side effects that range from minor and reversible to serious and irreversible. Broadening the recommendations in cholesterol lowering guidelines to include statin therapy for low risk individuals will unnecessarily increase the incidence of adverse effects without providing overall health benefit.

From a pharmacoeconomic perspective, expanding generic statin therapy to millions of low risk patients would add drug costs of up to \$1/day or more per person<sup>26</sup> for no net health benefit. Furthermore, if cholesterol lowering becomes established in low risk people, the indications for new, more expensive cholesterol lowering drugs such as the ApoB Antisense drugs and PCSK9 inhibitors currently being tested in clinical trials will probably expand as well.

The dominance of industry sponsored clinical trials of cardiovascular prevention has produced a body of scientific evidence that largely limits clinicians’ interventions to drug therapy.<sup>27</sup> Rather than being compelled by guidelines to prescribe statin therapy for people at low risk of cardiovascular disease, doctors would provide a far greater service by explaining the magnitude of the benefits and uncertainty about the harms of statins together with discussion of the epidemiological evidence showing that behavioural risk factors—including tobacco use, lack of physical exercise, and unhealthy diet—are responsible for 80% of cardiovascular disease (box).<sup>28</sup>

Contributors and sources: HGR is founder and former coordinator of the health and society programme at York University, Toronto. JDA and JMW have both written about cholesterol guidelines. JMW is coordinating editor of the Cochrane hypertension review group. NJ has extensive experience in the design, analysis, and interpretation of data arising from clinical trials and epidemiological studies of both infectious and chronic diseases. This article was prompted by a conversation about the 2013 Cochrane review’s reliance on the CTT findings for conclusions about statins in low risk people. JDA drafted the initial manuscript, which was extensively reviewed and revised based on input from the other authors, and is the guarantor.

Competing interests: All authors have read and understood the BMJ Group policy on declaration of interests and declare the following interests: JDA and NJ serve as experts for plaintiffs’ attorneys in litigation involving the drug industry (including a statin). JDA has received payment for lectures from several universities, medical schools, and non-profit organisations. He was formerly executive director of health management for Wells Fargo Health Solutions.

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**What low risk patients need to know**

- Lifestyle factors—including lack of exercise, tobacco use, and unhealthy diet—account for 80% of cardiovascular disease
- For people at low risk of cardiovascular disease (<10% risk over next five years), statins do not reduce the overall risk of death or serious illness
- In order to prevent one heart attack or stroke, 140 low risk people (< 10% five year risk) must receive statins for five years
- The side effects of statins—including muscle symptoms, increased risk of diabetes (especially in women), liver inflammation, cataracts, decreased energy, sexual dysfunction, and exertional fatigue—occur in about 20% of people treated with statins

28 World Health Organization. Global status report on noncommunicable diseases. 2010. [http://whqlibdoc.who.int/publications/2011/9789240686458\\_eng.pdf](http://whqlibdoc.who.int/publications/2011/9789240686458_eng.pdf).

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## Table

**Table 1 | Comparative all cause mortality for low risk patients in statin studies included in Cholesterol Treatment Trialists' meta-analysis<sup>8</sup>**

Five year risk of major vascular event	No of deaths/No of patients*		Relative risk (95% confidence interval)
	Treatment (statin or more statin) group	Control (no statin or less statin) group	
<5%	195/11 063	193/11 489	1.05 (0.86 to 1.28)
5% to <10%	580/13 095	639/13 037	0.90 (0.81 to 1.01)
Total	775/24 158	832/24 526	0.95 (0.86 to 1.04)

\*The numerator of each cell is the sum of "any vascular death" plus "non-vascular death" for the respective risk levels in the two sections of all participants data presented in figure 3 of the 2012 CTT meta-analysis. The denominator was derived by dividing the number of events by the "% per annum" for the same groups as the numerator and multiplying by 100 to determine total number of patient years in studies. We then divided that by the median number of years that the studies lasted (4.0 years for <5% five year risk of major vascular event, and 4.3 years for 5% to <10% risk) to determine number of patients in all studies; we averaged the denominators for each risk group to minimise rounding errors.

# OBSERVATIONS

## FROM THE HEART

### Saturated fat is not the major issue

Let's bust the myth of its role in heart disease

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Scientists universally accept that trans fats—found in many fast foods, bakery products, and margarines—increase the risk of cardiovascular disease through inflammatory processes.<sup>1</sup> But “saturated fat” is another story. The mantra that saturated fat must be removed to reduce the risk of cardiovascular disease has dominated dietary advice and guidelines for almost four decades.

Yet scientific evidence shows that this advice has, paradoxically, increased our cardiovascular risks. Furthermore, the government's obsession with levels of total cholesterol, which has led to the overmedication of millions of people with statins, has diverted our attention from the more egregious risk factor of atherogenic dyslipidaemia.

Saturated fat has been demonised ever since Ancel Keys's landmark “seven countries” study in 1970.<sup>2</sup> This concluded that a correlation existed between the incidence of coronary heart disease and total cholesterol concentrations, which then correlated with the proportion of energy provided by saturated fat. But correlation is not causation. Nevertheless, we were advised to cut fat intake to 30% of total energy and saturated fat to 10%.<sup>3</sup> The aspect of dietary saturated fat that is believed to have the greatest influence on cardiovascular risk is elevated concentrations of low density lipoprotein (LDL) cholesterol. Yet the reduction in LDL cholesterol from reducing saturated fat intake seems to be specific to large, buoyant (type A) LDL particles, when in fact it is the small, dense (type B) particles (responsive to carbohydrate intake) that are implicated in cardiovascular disease.<sup>4</sup>

Indeed, recent prospective cohort studies have not supported any significant association between saturated fat intake and cardiovascular risk.<sup>5</sup> Instead, saturated fat has been found to be protective. The source of the saturated fat may be important. Dairy foods are exemplary providers of vitamins A and D. As well as a link between vitamin D deficiency and a significantly increased risk of cardiovascular mortality, calcium and phosphorus found commonly in dairy foods may have antihypertensive effects that may contribute to inverse associations with cardiovascular risk.<sup>6-8</sup> One study showed that higher concentrations of plasma *trans*-palmitoleic acid, a fatty acid mainly found in dairy foods, was associated with higher concentrations of high density lipoprotein, lower concentrations of triglycerides and C reactive protein, reduced insulin resistance, and a lower incidence of diabetes in adults.<sup>9</sup> Red meat is another major source of saturated fat. Consumption of processed meats, but not red meat, has been associated with coronary heart disease and diabetes mellitus, which may be explained by nitrates and sodium as preservatives.<sup>10</sup>

The notoriety of fat is based on its higher energy content per gram in comparison with protein and carbohydrate. However, work by the biochemist Richard Feinman and nuclear physicist Eugene Fine on thermodynamics and the metabolic advantage of different diet compositions showed that the body did not metabolise different macronutrients in the same way.<sup>11</sup> Kekwick and Pawan carried out one of the earliest obesity experiments, published in the *Lancet* in 1956.<sup>12</sup> They compared groups consuming diets of 90% fat, 90% protein, and 90% carbohydrate and showed that the greatest weight loss was in the fat consuming group. The authors concluded that the “composition of the diet appeared to outweigh in importance the intake of calories.”

The “calorie is not a calorie” theory has been further substantiated by a recent *JAMA* study showing that a “low fat” diet resulted in the greatest decrease in energy expenditure, an unhealthy lipid pattern, and increased insulin resistance in comparison with a low carbohydrate and low glycaemic index diet.<sup>13</sup> In the past 30 years in the United States the proportion of energy from consumed fat has fallen from 40% to 30% (although absolute fat consumption has remained the same), yet obesity has rocketed.

One reason: when you take the fat out, the food tastes worse. The food industry compensated by replacing saturated fat with added sugar. The scientific evidence is mounting that sugar is a possible independent risk factor for the metabolic syndrome (the cluster of hypertension, dysglycaemia, raised triglycerides, low HDL cholesterol, and increased waist circumference).

In previous generations cardiovascular disease existed largely in isolation. Now two thirds of people admitted to hospital with a diagnosis of acute myocardial infarction really have metabolic syndrome—but 75% of these patients have completely normal total cholesterol concentrations.<sup>14</sup> Maybe this is because total cholesterol isn't really the problem?

The Framingham heart study sanctified total cholesterol as a risk factor for coronary artery disease, making statins the second most prescribed drug in the US and driving a multibillion dollar global industry. In the United Kingdom eight million people take statins regularly, up from five million 10 years ago. With 60 million statin prescriptions a year, it is difficult to demonstrate any additional effect of statins on reduced cardiovascular mortality over the effects of the decline in smoking prevalence and primary angioplasty.<sup>15</sup>

Despite the common belief that high cholesterol is a significant risk factor for coronary artery disease, several independent population studies in healthy adults have shown that low total cholesterol is associated with cardiovascular and non-cardiac mortality, indicating that high total cholesterol is not a risk factor in a healthy population.<sup>16-18</sup>

A recent “real world” study of 150 000 patients who were taking statins showed “unacceptable” side effects—including myalgia, gastrointestinal upset, sleep and memory disturbance, and erectile dysfunction—in 20% of participants, resulting in discontinuation of the drug.<sup>19</sup> This is massively at odds with the major statin trials that report significant side effects of myopathy or muscle pain in only one in 10 000.

A meta-analysis of predominantly industry sponsored data reported that in a low risk group of people aged 60-70 years taking statins the number needed to treat (NNT) to prevent one cardiovascular event in one year was 345.<sup>20</sup> The strongest evidence base for statins is in secondary prevention, where all patients after a myocardial infarction are prescribed maximum dose treatment irrespective of total cholesterol, because of statins' anti-inflammatory or pleiotropic (coronary plaque stabilising) effects. In this group the NNT is 83 for mortality over five years. This doesn't mean that each patient benefits a little but rather that 82 will receive no prognostic benefit.<sup>21</sup> The fact that no other cholesterol lowering drug has shown a benefit in terms of mortality supports the hypothesis that the benefits of statins are independent of their effects on cholesterol.

Adopting a Mediterranean diet after a heart attack is almost three times as powerful in reducing mortality as taking a statin. The recently published PREDIMED randomised controlled trial was stopped early after it showed that in high risk people the Mediterranean diet achieved a 30% improvement over a “low fat” diet in terms of cardiovascular events.<sup>22</sup>

Pharmacotherapy can assuage the symptoms but can't alter the pathophysiology. Doctors need to embrace prevention as well as treatment. The greatest improvements in morbidity and mortality have been due not to personal responsibility but rather to public health. It is time to bust the myth of the role of saturated fat in heart disease and wind back the harms of dietary advice that has contributed to obesity.

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