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Should statins be prescribed to people at low risk of cardiovascular disease?

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

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).[1] 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."[2] This conclusion was consistent with the 2006-08 guidance from the National Institute for Health and Care Excellence (NICE)[3] 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.[4]

If risk is estimated using the QRISK2 score,[5] by the 2011 standards just 2% of women in their 50s and 16% in their 60s qualify for statin therapy (≥ 20% 10 year risk of cardiovascular disease). For men, 9% in their 50s and 48% in their 60s qualify.[6] 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.[1 7] 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.

The endpoint that is most encompassing, and least subject to bias, in statin trials is all cause mortality

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.[8]

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%,[9] in 27 clinical trials that had been published by the end of 2009.[10] 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.[5] 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).

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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

Our calculations (table) 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.[9] 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.[11]

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.[12]

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.[13] 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.[14]

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.[15]

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[16]—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

Comparative all cause mortality for low risk patients in statin studies included in Cholesterol Treatment Trialists' meta-analysis[8]

Five year risk of major vascular event	No of deaths/No of patients*		
	Treatment (statin or more statin) group	Control (no statin or less statin) group	Relative risk (95% confidence interval)
<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.

Health Initiative trial show a 48% increase in the risk of new onset diabetes associated with statins in postmenopausal women.[17]

Others

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

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.[22]

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).[23]

In community based studies of drug use, at least 50% of patients discontinue statin therapy within one year

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."[1] 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%.[24] 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.[25]

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[26] 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 Antisence 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.[27] 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).[28]

WHAT LOW RISK PATIENTS NEED TO KNOW

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- 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

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Competing 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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