



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

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

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

Despite a small CV benefit, John Abramson, Harriet Rosenberg, and Jim Wright show statins do not provide overall health benefit for people at low risk

John Abramson *lecturer*,<sup>4</sup> \* Harriet G. Rosenberg *professor emeritus*<sup>5</sup>, James Wright *managing director and chair*<sup>6</sup>

The 2011 Cochrane Review that addressed the benefit of statins for the primary prevention of coronary artery disease retreated from the recommendations of the 2001 U.S. National Cholesterol Education Program guidelines, concluding:

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>1</sup>

The review stated that existing evidence did not support the use of cholesterol-lowering statin for people with less than a 2% per year risk of cardiovascular disease (CVD). This conclusion was consistent with the 2008 guidance from the National Institute of Clinical Excellence (NICE)<sup>2</sup> and the 2011 update of the American Heart Association's Guidelines for the Prevention of Cardiovascular Disease in Women (see Table 4), both of which recommended statin therapy only when 10-year risk of CVD is greater than 20%.<sup>3</sup> (Based on the results of the JUPITER trial, these guidelines added that statin therapy "could be considered" for women over 60 with estimated 10-year CHD risk of >10% and hsCRP is >2 mg/dL after lifestyle modification). The 2011 Cochrane Review also noted that the removal of patients with co-morbidities from clinical trials of statins limits the generalizability of their results to the broader population that would be treated with statins in the real world.

In 2013 the Cochrane Review was updated with a radically different conclusion that applied to all people, even those with <1% per year risk of CVD:

The individual patient data meta-analyses now provide strong evidence to support [statin] use in people at low risk of cardiovascular disease.<sup>4</sup>

This abrupt change was not based on new data from randomized controlled trials. Rather, the 2013 Cochrane review stated that its previous conclusion about the use of statins for people at low risk of CVD "is no longer tenable in light of the CTT [Cholesterol Treatment Trialists] Collaboration findings." The 2013 Cochrane review concluded that the findings of the CTT

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3 meta-analysis countered concerns about the effect of statins in low-risk groups and that “the  
4 benefits of statins outweigh any risks of serious adverse effects since no increase in cancers was  
5 found and all-cause mortality was lower in those on statins.”  
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8 The 2013 Cochrane Review’s recommendation to extend statin therapy to low risk people will  
9 certainly be considered in the formulation of future cholesterol-lowering guidelines, but does the  
10 totality of evidence truly show greater benefit than harm of statin therapy in this population?  
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## 13 **2012 CTT Meta-analysis**

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15 The CTT patient-level meta-analysis published in 2012 assessed the net effects of cholesterol-  
16 lowering with statin therapy in people at low risk of CVD, 5-year risk < 10%, in 27 clinical trials  
17 that had been published through the end of 2009.<sup>1</sup> The authors concluded that statin therapy  
18 significantly reduces the relative risk of major vascular events—including major coronary events  
19 (non-fatal myocardial infarction or coronary death), strokes and coronary revascularization  
20 procedures—by about 20% per 1.0 mmol/L reduction in LDL cholesterol, regardless of risk  
21 level.  
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26 Further, the authors concluded that statin therapy reduced the risk of major coronary events even  
27 in low risk patients – those with 5-year CV risk < 10%, whose average 5-year risk is 2.6%. In  
28 this risk category, statin therapy prevented 11 major vascular events per 1000 people treated for  
29 5 years. This statistically significant CV benefit of statins in low risk patients was deemed by  
30 CTT authors to “greatly [exceed] any known hazards of statin therapy.”  
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34 Based on these analyses, the CTT authors concluded that current guidelines should be  
35 reconsidered because of the documented benefit of statin therapy in low-risk people with 5-year  
36 risk of major vascular event lower than 10%.  
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## 39 **All-Cause Mortality**

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41 The most encompassing and least subject to bias endpoint in statin trials is all-cause mortality<sup>5</sup>  
42 —rarely misdiagnosed and not subject to inaccurate determination of cause. The following  
43 table, presenting all-cause deaths in low-risk patients (< 5% and ≥5% to <10% over 5 years), is  
44 reconstructed from data in Figure 3 of the 2012 CTT publication:  
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48 TABLE.

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50 Thus, the patient-level data included in the CTT meta-analysis does not show that preventive  
51 statin therapy significantly reduces overall mortality in people with < 10% 5-year risk of major  
52 CV event.  
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55 Persistence of lower all-cause and CV mortality was suggested by meta-analysis of published  
56 long-term open label follow-up of lipid-lowering clinical trials.<sup>6</sup> However, out of a total of 459  
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statin trials only 8 trials published follow-up data, each of which was based on post hoc analysis. Six of the eight studies were commercially funded, and conflicts of interest in authors were not disclosed in the other two. Such a small and highly self-selected publication of post hoc analyses does not constitute significant evidence of benefit.

## “Hard” Cardiovascular Endpoints

After all-cause mortality, the “hard” CV endpoints—CV death, myocardial infarction, and stroke—are the most reliable because they minimize subjective input and are least vulnerable to bias in adjudication.<sup>7</sup> In addition, “hard” CV endpoints are most important because they permanently impact people’s lives. Some studies, including CTT publications, have increased statistical power by including “softer” outcomes, like coronary revascularization procedures. However, rates of revascularizations are less precise because of geographical variations in thresholds for intervention and because treatment allocation is largely unblinded based on the lower total and LDL cholesterol levels in people assigned to the statin-treatment arms of the clinical trials. Bias due to unblinding has been documented for outcomes other than all-cause mortality and noted particularly with subjectively determined outcomes.<sup>8</sup>

In the CTT meta-analysis approximately 40% of the “major vascular events” that occurred in people with a 5-year CV risk of <10% were coronary revascularization procedures.<sup>9</sup> Thus, the absolute reduction of major coronary events and stroke was between 6.6 and 11 per 1000 low-risk patients treated for 5 years. In other words, between 91 and 152 low risk people need to be treated with statin for 5 years in order to prevent one major coronary event or stroke.

## Serious Adverse Events

Total serious adverse events (SAEs)—which include death, hospitalization, prolongation of hospitalization, cancer, or permanent disability—provide the best indication of the net effect of a treatment on overall health. Despite having access to patient-level data, the CTT meta-analysis was silent on the effect of statin therapy on SAEs. Among the 5 largest trials included in the meta-analysis, 3 reported no reduction in SAEs associated with statin therapy (JUPITER, ASCOT, LIPID) and two failed to report SAEs (HPS and ALLHAT). The updated Cochrane Review relied upon two prior reviews, based on published data only, to conclude the rate of SAEs was similar in statin and placebo groups. Cost-effective analysis based on reduction in CV events without consideration of overall rates of SAEs is meaningless—all SAEs are costly. Moreover, with no reduction in all-cause mortality and no evidence of reduction in serious adverse events for patients with 5-year CV risk of < 10%, the net benefit/harm equation has zero overall benefit and ignores the clear evidence of harm that has been demonstrated in clinical trials and observational studies.

## Adverse Events

## Myopathy

The excess risk of myopathy associated with statin therapy reported in the CTT meta-analysis is 0.5 per 1000 patients—number needed to harm (NNH) is 2000. However, a cross-sectional analysis from the National Health and Nutrition Examination Survey (NHANES) database shows that the frequency of muscle symptoms associated with statin use is 100 times greater than reported in clinical trials—53 per 1000 patients, NNH is 19.<sup>10</sup> A retrospective cohort study that included 13,626 statin users and 3 times more non-users found a greater incidence musculoskeletal disorders and injuries in statin users compared to non-statin users: OR 1.19 (1.08-1.3) and 1.13 (1.05-1.21), respectively. The NNH for musculoskeletal injuries and symptoms in people taking statins was 37 and 47, respectively.<sup>11</sup>

Pathologic findings are consistent with symptomatic statin-induced myopathy. Structural damage of skeletal muscle fibers (breakdown of the T-tubular system) has been documented in both asymptomatic<sup>12</sup> and symptomatic<sup>13</sup> statin-treated patients with normal creatinine kinase levels. Similar pathological changes were induced by extraction of cholesterol from muscle fibers *in vitro*, suggesting that cholesterol-lowering itself plays a role in muscle cell injury. Mitochondrial dysfunction was found in all 4 patients who repeatedly distinguished statin vs. placebo therapy based on muscle symptoms.<sup>14</sup>

Simvastatin 40 mg/day significantly attenuated improvement in cardiorespiratory fitness in 18 in overweight or obese patients compared to 19 treated with placebo,  $p < 0.005$ .<sup>15</sup>

## Diabetes

CTT authors reported a 10% increase in the relative risk of developing diabetes while on statin therapy, corresponding to 1 excess new diagnosis per 1000 statin-treated people per year. However, data from the JUPITER trial show the risk of diabetes associated with statin therapy in women was increased by 50%, corresponding to 11 new diagnoses per 1000 statin-treated women over 1.9 years<sup>16</sup>—more than 5 times the frequency reported by CTT. Similarly, observational data from the Women's Health Initiative trial show a 48% increase in the risk of new onset diabetes associated with statin therapy 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 cataract;<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, decreased risk of esophageal cancer associated with statin use has been noted.<sup>17</sup>

## Potential Sources of Bias in Statin Clinical Trials

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3 All but one of the RCTs included in the CTT meta-analysis were funded by the manufacturer of  
4 the statin being studied.<sup>4</sup> A recent Cochrane Review found that industry sponsored clinical trials  
5 are significantly more likely than non-commercially funded studies to report favorable efficacy  
6 and safety results and conclusions.<sup>22</sup>  
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10 Possible mechanisms by which adverse effects might be minimized in clinical trials include:  
11 exclusion of up to 30% patients with co-morbidities, pre-randomization run-in periods in which  
12 people who fail to tolerate statin therapy are excluded, 10% drop-out rates, failure to assess for  
13 specific potential adverse events (like myopathy or cognitive changes), and selective reporting of  
14 adverse events (including serious adverse events).<sup>23</sup>  
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17 The Cochrane authors acknowledge that:

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19 The reporting of adverse events in these trials is generally poor, with failure to provide  
20 details of severity and type of adverse events or to report on health-related quality of life.  
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23 Nevertheless, the 2013 Cochrane review concluded that even in the absence of high quality  
24 evidence it is “unlikely” that any “major life-threatening hazards associated with statin use  
25 exist.” However, the large discrepancies between the frequency of adverse events reported in  
26 commercially funded RCTs included in CTT meta-analyses and non-commercially funded  
27 studies show that determination of the harm side of the benefit/harm equation cannot be left to  
28 industry.  
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## 32 **Conclusion**

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34 Attention is being too narrowly focused on the impact of statins on cardiovascular disease in  
35 people at low-risk of CV disease. The best available evidence shows that in this population,  
36 statin therapy prevents one serious cardiovascular event in approximately 100 people treated for  
37 5 years. However, for these people statin therapy does not reduce the overall risk of death or  
38 serious illness, and has a real risk of causing side effects that range from minor and reversible to  
39 serious and irreversible. Therefore, broadening the recommendations for statin treatment for low  
40 risk individuals in cholesterol-lowering guidelines will unnecessarily increase the incidence of  
41 adverse effects and healthcare costs without providing overall health benefit.  
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46 Rather than being compelled by guidelines to prescribe statin therapy, doctors would be of far  
47 greater service to people at low-risk of CV disease by engaging with them in therapeutic  
48 partnerships.<sup>24</sup> In place of paternalistically dictating statin therapy, doctors would explain the  
49 true benefits and harms of statins as well as the more compelling epidemiologic evidence  
50 showing the cardiovascular (and more general) benefit of healthy lifestyle habits. Patients would  
51 be encouraged to share their personal concerns and preferences beyond a simple focus on  
52 cholesterol numbers. Then each patient/doctor partnership could focus on the most important  
53 cardiovascular intervention: providing ongoing support to facilitate transition to the healthier  
54 lifestyle habits that would most effectively optimize overall health and well-being.  
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### Key Messages

- In low risk people, statin therapy provides a significant but small reduction in major CV events, NNT  $\approx$  100 per 5 years
- Statin therapy does not reduce all-cause mortality or serious adverse events in the low risk population
- Incidence of harms caused by statins in clinical trials is under-reported
- Because the balance of overall benefit to harm for statin therapy in low risk people is not positive, guidelines should not recommend statin therapy for this population

Conflict of Interest Disclosures: Dr. Abramson serves as an expert for plaintiffs' attorneys in litigation involving the pharmaceutical industry (including a statin), and has received payment for lectures from several universities, medical schools, and non-profit organizations. He formerly served as Executive Director of Health Management for Wells Fargo Health Solutions. Drs. Rosenberg and Wright have no potential conflicts of interest. None of the authors has relevant financial interests.

TABLE: COMPARATIVE ALL-CAUSE MORTALITY FOR  
LOW-RISK PATIENTS IN STATIN STUDIES

| Total Deaths<br>(5-year MVE risk) | Statin/more statin<br>Events/patients | Control/less statin<br>Events/patients | Relative risk (95%<br>CI) |
|-----------------------------------|---------------------------------------|--|---------------------------|
| Total Deaths                      |                                       |  |                           |
| <5%                               | 195/11063                             | 193/11489                              | RR 1.05 (0.86,1.28)       |
| $\geq$ 5% to <10%                 | 580/13095                             | 639/13037                              | RR 0.90 (0.81, 1.01)      |
| Total < 10%                       | 775/24158                             | 832/25526                              | RR 0.94 (0.85-1.03)       |

Legend: Derivation of table presenting all-cause mortality for low risk patients: 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 Table 3 of the 2012 CTT meta-analysis. The denominator for each cell was derived by a) dividing the number of events by "% per annum" and multiplying by 100 for each cell of the two "total participants" sections of Table 3 for the risk groups < 5% 5-years risk of major vascular event and  $\geq$  5% to < 10% risk to determine total number of patient-years in studies; b) dividing that by the median number of years that the studies lasted (4.0 years for < 5% 5-year risk of major vascular event, and 4.3 years for  $\geq$  5% to < 10% risk people) to determine number of patients in all studies; and c) averaging the denominators for each risk group to minimize rounding errors. Statistics were calculated on openepi.com.

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