

Are Lipid lowering (Statins) Guidelines Evidence-Based? Lancet

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The authors argue that recommendations for the expanded use of statins to stave off cardiovascular disease are NOT supported by the evidence.

A Commentary in the Lancet by John Abramson, MD, of Harvard Medical School, author of *Overdosed America*, and James Wright, MD, University of British Columbia, challenges the validity of the U.S. clinical practice guidelines recommending the expanded use of statins by healthy people.

It should be noted that: "For adults aged between 30 and 80 years old who already have occlusive vascular disease, statins confer a total and cardiovascular mortality benefit and are not controversial."

But the revised U.S. guidelines (2001) increased the target population to be treated with statins from 13 million to 36 million Americans. That increase offers huge economic implications for the manufacturers of statins.

The guidelines, the authors say, "are based on the assumption that cardiovascular risk is a continuum and that evidence of benefit in people with occlusive vascular disease (secondary prevention) can be extrapolated to primary prevention populations. This assumption, plus the assumption that cardiovascular risk can be accurately predicted, leads to the recommendation that a substantial proportion of the healthy population should be placed on statin therapy."

The controversy involves this question: which people without evident occlusive vascular disease (true primary prevention) should be offered statins? The authors note that in formulating recommendations for primary prevention, the authors of the guidelines did not rely on the data that already exist from the primary prevention trials. Indeed, the authors note that the guidelines cite seven and nine randomised trials, in support of statin therapy for the primary prevention of this disease in women and people aged over 65 years. Yet NOT ONE of the studies provides such evidence.

Furthermore, they note: "the absolute risk reduction of 1.5% is small and means that 67 people have to be treated for 5 years to prevent one such event. Further analysis revealed that the benefit might be limited to high-risk men aged 30-69 years. Statins did not reduce total coronary heart disease events in 10,990 women in these primary prevention trials. Similarly, in 3,239 men and women older than 69 years, statins did not reduce total cardiovascular events (relative

"Our analysis suggests that lipid-lowering statins should not be prescribed for true primary prevention in women of any age or for men older than 69 years. High-risk men aged 30-69 years should be advised that about 50 patients need to be treated for 5 years to prevent one event."

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Comment
Are lipid-lowering guidelines evidence-based?

The last major revision of the US guidelines, in 2001,¹ increased the number of Americans for whom statins are recommended from 13 million to 36 million, most of whom do not yet have but are estimated to be at moderately elevated risk of developing coronary heart disease.² In support of statin therapy for the primary prevention of this disease in women and people aged over 65 years, the guidelines cite seven and nine randomised trials, respectively. Yet not one of the studies provides such evidence.

For adults aged between 30 and 80 years old who already have occlusive vascular disease, statins confer a total and cardiovascular mortality benefit and are not controversial. The controversy involves this question: which people without evident occlusive vascular disease (true primary prevention) should be offered statins? With about three-quarters of those taking statins in this category,³ the answer has huge economic and health implications. In formulating recommendations for primary prevention, why do authors of guidelines not rely on the data that already exist from the primary prevention trials?

We have pooled the data from all eight randomised trials that compared statins with placebo in primary prevention populations at increased risk.⁴ Unfortunately, our analysis is imperfect because these trials are not solely primary prevention: 8.5% of patients had occlusive vascular disease at baseline.⁵ We used two outcomes to estimate overall benefit (benefit minus harm): total mortality and total serious adverse events (SAEs). Total mortality was not reduced by statins (relative risk 0.95, 95% CI 0.89-1.01). In the two trials that reported total SAEs, such events were not reduced by statins (1.01, 0.97-1.05) (data on SAEs from the other trials were not reported).

The frequency of cardiovascular events, a less encompassing outcome, was reduced by statins (relative risk 0.82, 0.77-0.87). However, the absolute risk reduction of 1.5% is small and means that 67 people have to be treated for 5 years to prevent one such event. Further analysis revealed that the benefit might be limited to high-risk men aged 30-69 years. Statins did not reduce total coronary heart disease events in 10 990 women in these primary prevention trials (relative risk 0.98, 0.85-1.12).⁶ Similarly, in 3239 men and women older than 69 years, statins did not reduce total cardiovascular events (relative risk 0.94, 0.77-1.15).⁷

Our analysis suggests that lipid-lowering statins should not be prescribed for true primary prevention in women of any age or for men older than 69 years. High-risk men aged 30-69 years should be advised that about 50 patients need to be treated for 5 years to prevent one event. In our experience, many men presented with this evidence do not choose to take a statin, especially when informed of the potential benefits of lifestyle modification on cardiovascular risk and overall health.⁸

This approach, based on the best available evidence in the appropriate population, would lead to statins being used by a much smaller proportion of the overall population than recommended by any of the guidelines.⁹

Why the disagreement?

The current guidelines are based on the assumption that cardiovascular risk is a continuum and that evidence of benefit in people with occlusive vascular disease (secondary prevention) can be extrapolated to primary prevention populations. This assumption, plus the assumption that cardiovascular risk can be accurately predicted, leads to the recommendation that a substantial proportion of the healthy population should be placed on statin therapy.

A similar set of assumptions underlie the conclusions of the Cholesterol Treatment Trialists' (CTT) collaboration, a group that undertakes periodic meta-analyses of individual participants' data on morbidity and mortality from all relevant large-scale randomised trials of lipid-modifying treatment.⁵ The CTT Collaborators included seven trials of statins for

secondary prevention and seven trials of statins for mostly primary prevention.

However, instead of analysing these two groups of studies separately, they combine all the studies and report the overall effect. Because they have individual participants' data, the CTT Collaborators have the unique opportunity to analyse the data for the 41 354 people in the true primary prevention group that they have identified as included in these studies.⁵ However, they do not report on this pure primary prevention population. Instead they calculate and report the absolute benefit of statins in 47 925 patients with no coronary heart disease at baseline; however, this group includes about 6570 patients with pre-existing cerebrovascular or peripheral vascular disease. Combination of these secondary prevention patients (5-year frequency of major vascular events 25-30%) with the true primary prevention group (5-year incidence of major vascular events 9%) inflates the estimate of absolute benefit from 1.5% (our estimate) to 2.5%.

The CTT collaborators have primary prevention outcome data that can resolve the issues we raise. Subpopulations of particular interest include: men, women, men aged 70 years or older, women below the age of 70 years, people with diabetes mellitus, 20% of people with the lowest bodyweight, people taking more than five drugs, and tertiles of cardiovascular risk at baseline. The following are the outcomes that would be most informative: total mortality, total SAEs, total incidence of cancer, and total cardiovascular events. This analysis would answer the key outstanding questions.

First, do the data on primary prevention confirm that there is no overall benefit in adult women of any age and in men aged 70 years and older? And, second, is there significant heterogeneity between the statin treatment effect in primary prevention subgroups compared with that in secondary prevention subgroups? If the answer to both these questions is yes, the assumption that the benefits for secondary prevention populations can be extrapolated to primary prevention populations is false and the cholesterol treatment guidelines based on this assumption should be revised.

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JMW declares no conflict of interest. JA is an expert consultant to plaintiffs' attorneys on litigation involving the drug industry, including Pfizer for its marketing of atorvastatin.

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