Considerable uncertainty remains in the evidence for primary prevention of cardiovascular disease

By: Carl Heneghan
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Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide,[1] and therefore strategies that aim to improve prevention in people without existing disease (primary prevention) are important for managing the overall burden of disease. This edition of *The Cochrane Library* adds to the evidence-base in this area with publication of two Cochrane Reviews on such preventive strategies: multiple risk factor interventions for primary prevention of coronary heart disease,[2] and statins for the primary prevention of CVD.[3]

Multiple risk factor interventions aim to alter modifiable risk factors such as smoking, hypertension, hyperlipidaemia, high intake of dietary salt, lack of exercise, obesity and high glucose levels in people with diabetes, which increase the risk of coronary heart disease. The Cochrane Review by Ebrahim and colleagues focuses on counselling and educational interventions, and includes 55 trials (an addition of 16 studies compared with the previous version of this review) aimed at modifying one or more cardiovascular risk factors in the adult general population.[2]

Disappointingly, the current evidence concluded that counselling and education to change behaviour do not reduce total or coronary heart disease mortality or clinical events in general populations. Despite this finding numerous guidelines continue to promote such interventions.[4] Yet, as the review notes, no large-scale randomised controlled trials have recently been undertaken to improve the evidence-base in this area. In addition, there were substantial shortcomings in the methods of the included trials, limiting the overall findings. For instance, in only 13 out of 55 trials the methods for random allocation were considered adequate; in nine they were found to be inadequate.

A number of reasons can explain why such interventions often prove ineffective. For instance, considerable variation often occurs in the components of the interventions, which are frequently poorly described.[5] This point is highlighted by the fact that very few of the older trials in the review provided sufficient descriptions of the interventions to allow replication, and in several studies the intervention varied between sites and over time.[2] This clinical heterogeneity makes pooled estimates of effect questionable. The review also found that only people with pre-existing disease such as hypertension or diabetes showed an effect with intervention, which might have been a result of an increase in adherence to pharmacological agents with behavioural interventions.[2] In addition, behavioural risk factor interventions are often labour-intensive and not sustainable over the long course, thus the effects dwindle over time.[6]

In the second Cochrane Review in this edition, which assessed statins for the primary prevention of CVD, 14 randomised controlled trials were included.[3] Eleven of these trials recruited patients with specific conditions such as raised lipids, diabetes or hypertension. While some trials entered participants with CVD, an arbitrary threshold of no more than 10% of participants with pre-existing disease was used for

inclusion of a trial in the review. This was to avoid major effects of treatment, which would bias the outcomes on those with existing CVD. Overall all-cause mortality was reduced by statins, as well as combined fatal and non-fatal cardiovascular endpoints, while no evidence of significant harm was observed. However, there was only limited evidence that primary prevention with statins may be cost-effective.

There are a number of concerning points with this review that arise due to limitations in the published data. First, in the majority of trials in the review power calculations were based on composite outcomes; second, in over one third of trials outcomes were reported selectively; and third, eight trials did not report on adverse events at all. This is unacceptable, as important data aiding the overall interpretation of the systematic review were not obtainable despite attempts to contact authors. Moreover, two large trials were prematurely stopped because significant reductions in primary composite outcomes had been observed. All of these shortcomings significantly undermine the findings of this review. To date only one trial has been publically funded, while the authors of nine trials reported having been sponsored either fully or partially by pharmaceutical companies.

The current Cochrane Review results for primary prevention using statins are at odds with previous reviews such as the Cholesterol Treatment Trialists' Collaboration's review.[7] This individual patient data review found large reductions in major vascular endpoints in the subgroup of people without previous myocardial infarction or history of coronary heart disease. However, the included population had either established vascular disease or were considered at high risk of first vascular event based on risk factors.[7] A second systematic review that included studies where at least 80% or more of the participants did not have established CVD found that statin use was associated with significantly improved survival and large reductions in the risk of major cardiovascular events.[8] Therefore, if participants with pre-existing CVD, or at high risk of disease, are included in primary prevention trials, their elevated baseline risk significantly affects the overall benefit to harm ratio for statin use.

The Cochrane Review guidance is helpful in highlighting that the current evidence does not support use of statins below a 1% annual all-cause mortality risk or an annual CVD event rate of below 2%.[3] This is aligned with NICE guidance, whereby statins should be used as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD.[9]

Although various multiple prevention strategies exist, the most effective and cost-effective intervention for primary prevention in adults at low risk currently remains unclear.[10] Because of this uncertainty, interventions targeting CVD risk reduction in low-risk population should be undertaken in the context of a randomised controlled trial; preventing scarce healthcare resources going to waste. Such trials should aim to exclusively recruit individuals without pre-existing disease. In interpreting the evidence-base, where observational studies show effects of such interventions, the major component of the effect is likely to be regression to the mean. It is therefore unwise to use such studies to determine the overall benefits and harms to the population at risk and drive policy.

Given the current limitations of the evidence-base, the alternative approach for policy is to focus on population-wide prevention. Widely publicised by Geoffrey Rose,[11] legislating for smoke-free public spaces, re-designing public spaces to improve exercise or reducing daily dietary salt intake prove generally effective and can be cost-saving interventions.[12] Given the scale of the worldwide CVD problem, large-scale commissioned studies of multiple risk factor interventions are urgently required.

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Contact the Editor in Chief, Dr David Tovey (dtovey@cochrane.org): Feedback on this editorial and proposals for future editorials are welcome.

Feedback on this editorial:

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Dr Heneghan presents an insightful editorial.[1] The way statin trial results are reported is indeed confusing, incomplete and thus problematic. My analysis is that statins are really glorified nitroglycerin mimics because of their undisputed NO/eNOS-promoting action. Statins, therefore, reduce angina- and coagulopathy-related effects, effectively all non-fatal, and thus, as well, their resulting interventions ... and more evidently so in men than in women where angina/nitrate-related effects are more diffuse.

What the editorial does not mention are differences with women, and where there is no doubt that there is no mortality benefit, as per at least three meta-analyses. Two of them found a relative risk [RR] of 1.00 versus placebo, including one including secondary prevention, and one concluding: "Our study showed that statin therapy reduced the risk of CHD events in men without prior cardiovascular disease, but not in women. Statins did not reduce the risk of total mortality both in men and women".[2][3][4]

Tellingly, in the past Drs Peto and Collins have told me that is would be inappropriate [*sic*] to release the four Kaplan-Meier mortality curves for the main Heart Protection Study Groups groups – men, women, diabetic and not. However, we know that end-of-trial female mortality was an insignificant p=0.08. Mostly, the suggested benefit for women by proponents is justified by 'proportional reductions' and by forest plots and calculations suggesting lack of heterogeneity with men ... yet the placebo-controlled randomised-trial reality is different.

Suggesting that women at any cardiac risk reduce all-cause deaths by taking statins is, at best, a statistics-derived artifact with unclear but massive numbers needed to treat, and at worst, a delusion or a deception. The reality: even in extreme-risk women in the much-cited 4S study,[5] there were three *more* deaths in women on statin than on placebo.

I suggest that in a next analysis women and men should be treated separately, and this regarding all single individual endpoints. The universally abused reporting item of "major cardiovascular events" should be banished, since it virtually always includes non-fatal angina-related effects, including medical decisions such as non-life-saving planned revascularisations. For example, in JUPITER, revascularisations were by far *the* major "event" benefit and, in women, the *only* significant one after 6500 on-statin years ... and cardiovascular mortality was not reduced in either men or women.[6]

When any-cause deaths are not reduced by drugs prescribed for a fatal disease, we are treating either lesser value effects, numbers in lab reports or other surrogate endpoints but not real causes.[7] That is the case for statins in women, a mathematical certainty.

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